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LYMPHOLOGY

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Editorial

The Mask Of Sanity

One of the underlying problems of medical students at this university, and perhaps at others, is the need to live up to unwritten standards of competence imposed upon them (and expected of them) by their professors and fellow students. It may be taken for granted too often that "competition" is a healthy driving force in the makeup of the student. This "competitive striving" with fellow peers, must, after all, later be rechannelled into a spirit of co-operation with other members of the health team in the management of the patient. Most of us can detect in our confrères manifestations of the three basic orientations postulated by the late psychologist Karen Horney: the need to move *toward* people (approval); the need to move *away* from people (independence); and the need to move *against* people (competition). Theoretically, if any of these needs are ungratified, anxiety results; this does occur in many students and often justifiably. Apart from understandable and acceptable situations such as final examinations, most of us can easily cover up our anxieties in our behaviour towards others with a host of well-developed and at times even contrived defense mechanisms ("I don't care if I fail; this exam doesn't count anyway.") After all, the medical student is an extraordinarily proud beast who abhors the thought of others laughing at his ill-thought out answer at the bedside clinic in front of fellow students, knowledgeable clinicians and, worst of all, the patient. The need for peer group approval, whether it be from the Chief of Surgery or from the junior interne, stems from a basic feeling of inferiority (or, a reactive 'superiority'): an inability to master the large volume of facts expected of him; the frustration of continually forgetting these facts and the inability to apply them to clinical situations; and the lack of confidence in dealing with the actual sick patient instead of a multiple choice question. Punishment for these *crimes* may be in the form of lower marks, forced anonymity by the rest of the 'team' on the ward (I want you boys to really involve yourself; you are an integral part of the 'team'), or unwarranted, sometimes false self deprecation ("I don't know anything!"). In addition, there is the fear of being wrong in any direct confrontation with the examiner or the clinician, especially when a positive decision requiring experience is needed. Students can beat the system with such stratagems as avoiding the 'examiner's' glance for fear of being asked a question; or hedging around the question by padding the answer with irrelevant facts the student does in fact know. Another trick, used to impress the clinician, is to ask an erudite question of *him*, the answer to which the student is already aware. How much of all this is related to the present system of evaluation by marks is uncertain.

The need for *independence* may be reflected in the increasing tendency to get away from the site of one's undergraduate training. Although a desire to 'see how other centres operate' is often cited as the positive reason for leaving, the primary reason is often negative—a disillusionment with the whole system, (although this is not meant to condemn the system *in toto*). A medical school should not function to foster anxiety. The graduate should be able to recall it as a place where learning was a pleasure.

Finally, the need to move *against* people, or *compete*, has long been promoted not only at medical school but in all other areas where intelligent people are pursuing their goals. The striving for marks is, unfortunately for some, overly stressful; it discourages experimentation and leads to a concentration on answers rather than problems. Many teachers coach the students for tests and care more for the 'appearance' of knowledge than the real understanding. As a result, there is less enjoyment in the learning process than is desirable—after all, the only answer that really sticks in one's mind is the answer to a question one might ask of another or of himself. In a less strict context, the *way* a question is asked, not by *whom*, also has a better chance of sinking in.

Although no concrete solution to these problems can be offered, it is nevertheless worthwhile for the student to occasionally contemplate his many complaints on 'psychological' terms. It is hoped that this approach may provide a refreshing alternative to the current, rather tedious practice of distributing questionnaires to evaluate possible curriculum changes for the purpose of making the student happier. The basic problems will be the same regardless of curriculum changes. The student who first gains insight into his own basic needs will be better equipped to understand the common problems shared by other medical students, and the experience gained while dealing with them in this light will prove invaluable.

D.A.L. W.K.L.

The editors have calculated that 48 individuals have had a hand in writing, editing, or otherwise handling the affairs of Volume XLV. This adds up to a great deal of valuable experience for a significant number of undergraduate students. At first we were unsure of the impact of this publication on students and graduate subscribers. The response has been gratifying; most students who have taken time to read the Journal have found the material of interest and definite value. In addition, many extra copies have been requested by interested outside parties such as internes, residents, and various health organizations.

This venture has been and always will be a team effort. The inevitable frustrations in meeting deadlines, the eventual satisfaction in putting out a quality journal, and the willing cooperation received by our staff have all been extremely rewarding to the editors. Without the initiative and hard work of the associate and assistant editors, the excellent material would not have been assembled. Without the skills of Judy Wunderly and her capable staff of artists, the finishing touches could not be applied. The behind-the-scenes efforts of Bob Walker, Bob MacKenzie, Sherryn Levinoff, and especially Mike Rosenbluth have been too often unrecognized, but are now gratefully acknowledged. Finally, Roger and Konrad at the Maple Leaf Press deserve credit for their long hours spent, especially with untyped manuscripts, and for cheerfully complying to our constant demands.

We are confident that next year's editors Abe Chaiton and Paul Muller will produce another excellent Journal. Our best wishes are extended to them and we hope the assistance they receive will help them enjoy the editorialship as much as we did.

D.A.L. W.K.L.

Guest Editorial

Dr. Vera Peters was born in Weston, Ontario and spent her early years on her parents' farm home near the present location of New Woodbine Racetrack. She graduated from Weston High School in 1928 and entered her pre-medical training at the University of Toronto that year. Upon her graduation in 1934, she interned in Toronto and in 1937 began an apprenticeship in radiotherapy at the Toronto General Hospital. Her interests were focussed upon the treatment of malignant disease, as her mother, two sisters, and a brother had all been stricken with various fatal malignancies. During the 1940's she began retrospective studies on carcinoma of the breast and the lymphomas and her interest has concentrated on these entities since then. In 1950, the Peters' clinical staging technique for Hodgkin's Disease was published. This represented a remarkable advance in treatment of patients with Hodgkin's Disease. Today Dr. Peters is internationally recognized as one of the world's foremost authorities on Hodgkin's Disease. She currently is senior radiotherapist at the Ontario Cancer Institute, Princess Margaret Hospital, and is an associate professor of radiotherapy at the University of Toronto.

The lymphomas are an interesting but perplexing group of diseases with a wide spectrum of histological and clinical features. Many of the current concepts of the disease which are included in this journal will change from time to time as has been demonstrated in the past. Likewise the therapy of the lymphomas should be approached with an open mind. In our experience over the years, the yearly survival rates have slowly but steadily improved as the knowledge of the course of disease in each division of the lymphomas has improved.

Fortunately, many new methods of detecting 'occult' sites of disease have recently become available and a better assessment of the extent of disease at the time of diagnosis is now possible. Lymphography studies have also aided in the identification of pathways of spread in the lymphomas. In the clinical situation it has become apparent that the first recognized site of disease is rarely the primary site. 'A node in the neck, the most common initial finding, is nearly always a warning signal that disease in some other hidden area has been brewing for a much longer period'.

To pave the way for better therapy in the future, a complete clinical evaluation of each new patient is essential to-day. In time the accumulated data will allow a better interpretation of the 'natural' course of the disease.

M. V. Peters

The Lymphomas

N. R. Flett B.Sc. 6T8

INTRODUCTION

The lymphomas are primary malignant neoplasms of lymphoreticular tissue. They are characterized by painless enlargement of lymph nodes, and the nature of the disease process is such that every organ in the body may become infiltrated. The important malignant features of this neoplasm are: progressive lymph node enlargement, infiltration of tissues (local and widespread), and terminal cachexia, anemia and fever. Males predominate 2:1 in most of the lymphomas.

TYPES OF LYMPHOMA

The major recognized entities are:

1. Follicular Lymphosarcoma
2. Lymphosarcoma
3. Reticulum Cell Sarcoma
4. Hodgkin's Disease

Follicular Lymphosarcoma

This variety of lymphoma used to be designated Giant Follicle Lymphoma. Now it is recognized as a stage of lymphosarcoma with a "follicular" pattern, and as such it carries a better prognosis than lymphosarcoma. It comprises 7% of the lymphomas and the incidence increases with age.

Clinical Manifestations — Single lymph node enlargement in the cervical, inguinal, or axillary regions is the primary symptom. Constitutional symptoms are minimal, and skeletal or visceral involvement is quite rare.

Morbid Anatomy — Enlarged nodes are discrete, nontender, and freely moveable. Cut section shows the follicles to be more numerous than usual throughout the node, rather than just at the periphery. Uniformly large follicles replace the normal architecture and obliterate the sinusoids.

Evolution — Rarely the follicular pattern is retained until death, with dissemination to bone marrow and other tissues. In most instances the disease undergoes transition to lymphosarcoma or reticulum cell sarcoma, and then assumes the characteristics of that disease.

Lymphosarcoma

This disease comprises 20% of all lymphomas, and the incidence increases with age.

Clinical Manifestations — This disease begins with enlargement of a *group* of nodes in the neck, axilla, mediastinum or retroperitoneal region and soon becomes generalized. Thus, a variety of symptoms due to spread along main lymphatic trunks[6] are produced by means of pressure, obstruction, traction and invasion. The spleen is enlarged, and in 25% the bone marrow shows large lymphocytic deposits. Extranodal involvement of the tonsils, nasopharynx, bone, kidney, gastrointestinal tract, and skin is frequently seen. Terminally, constitutional complaints dominate the picture.

Morbid Anatomy — Early the lymph nodes are discrete and firm without hemorrhage or necrosis, but later with invasion and adhesions to surrounding tissues, 'matting' occurs and firmness becomes a prominent feature. The cut surface is homogeneous, white, and glistening ("fish flesh appearance"). Histologically the architecture is destroyed by sheets of lymphocytes and there is capsule penetration. Lymphosarcoma is divided into lymphoblastic and lymphocytic types depending upon the degree of cellular differentiation.

Evolution — After an initial period (brief or prolonged) in which the disease is localized, the sarcomatous involvement becomes generalized. The median survival for both types of lymphosarcoma is 30 months.[6] If lymphocytic leukemia is defined as greater than 30,000 WBC/cmm with a preponderance of lymphocytes, then in Rosenberg's series (1961) 12.6% of lymphosarcoma patients who present without leukemia will develop it. Other investigators have put the figure closer to 50%.

Reticulum Cell Sarcoma

This group comprises 6% of lymphomas, and again there is a steadily increasing incidence with age.

Clinical Manifestations — The patient presents with *many groups* of enlarged nodes, and there is soon rapid progression to extranodal involvement. As in lymphosarcoma, patients often present with enlarged nodes *and* extranodal involvement, the latter being the primary pattern of disease. Hepatomegaly is more frequent than in lymphosarcoma. Constitutional complaints dominate the symptomatology with fatigue, anorexia and weight loss progressing relentlessly in untreated cases. The patient may develop areas of marked pain from local involvement. Few (2%) develop leukemia.

Morbid Anatomy — The involved *groups* of nodes are large, discrete and soft early in the disease with a tendency to involve adjacent glands later. Cut section shows a shiny white (fish flesh) surface with some areas of necrosis and hemorrhage. Histologically, sheets of large, pale-staining, anaplastic and pleomorphic cells replace the normal architecture. Infrequent mitoses are seen amongst areas of necrosis and fibrosis. Median survival is 14 months.[6]

Hodgkin's Disease

This disease will be discussed in detail in the second part of this paper.

THE EVOLUTION OF THE CLASSIFICATION OF THE LYMPHOMAS

The First One Hundred Years

In January 1832, Thomas Hodgkin presented a discussion at Guy's Hospital, London "On some morbid appearances of the absorbent glands and spleen". Wilks (1865) reviewed Hodgkin's cases and decided that four of the seven cases were quite different and justified a title distinct from "Lardaceous Disease". He then added eleven (15 total) of his own cases "where the glands were enormously enlarged and the spleen contained a white deposit like suet, scattered through it" and gave the eponym to these cases of "Hodgkin's disease". Throughout the remainder of the 19th century pathologists were very interested in this disease, and a very significant distinction came in 1893. At that time Kundrat recorded many points of difference between lymphosarcoma and Hodgkin's disease, primarily with respect to the microscopic appearance and the spread of disease.

The next significant division of lymph node diseases came in 1932 when "retothelsarcom" (reticulum cell sarcoma) was split off as a separate entity distinct from lymphosarcoma and Hodgkin's disease.

The Recent Past

Within the last fifteen years attempts to classify the lymphomas have shifted remarkably so that the classifications now provide a clinically useful prognostic index.

Lumb (1954) separated the lymphomas into distinct entities by considering two histological features: (1) the predominant cell type, and (2) the degree of differentiation of that cell line. Then, in line with the characteristics of malignancy in general he associated a poor prognosis with undifferentiated cells, and a better prognosis with well differentiated cells. His classification is shown in Table I.

Legend:
A Hodgkin's Sarcoma
Lymphoblastic lymphosarcoma
Anaplastic reticulum cell sarcoma
B Lymphosarcoma
C Giant Follicle Lymphoma
D Hodgkin's Granuloma
E Hodgkin's Paragranuloma
F Reticulum cell Sarcoma

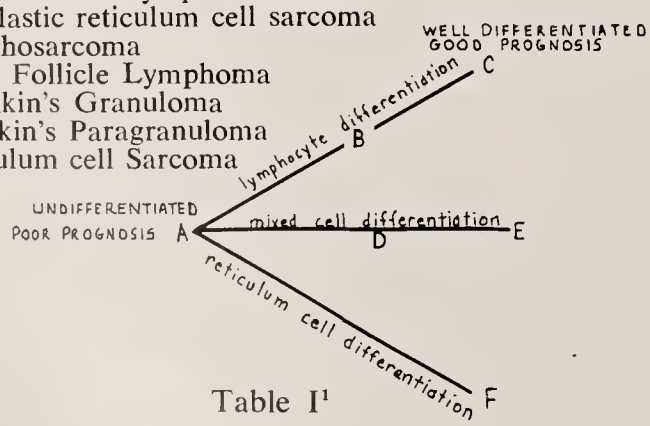

Table I[1]

Lumb's classification helped in our understanding of lymphomas and was easy to use in classical cases of disease. But unfortunately the lymphomas do not lend themselves to a simple 'pigeon hole' classification. Some of the unique features of lymphomas, not accounted for in Lumb's classification are:

(a) Lymphoma is not a single disease, but rather a spectrum.

(b) Lymphomas frequently show transition both clinically and pathologically from benign to more malignant states.

(c) Different morphological pictures can co-exist in a patient, and even in a given lymph node at the same time.

(d) This classification does not permit the recognition of borderline disease states, and thus results in much diagnostic confusion.

(e) With the deficiencies above, Lumb's classification is difficult to apply clinically.

Attempts to overcome these faults have been the goal in the derivation of the most recent concept of the lymphomas, which abandons the idea of lymphomatous disease as a distinct entity. The use of serial multiple biopsies at the site of disease has been most important in arriving at the present method of histological reporting. This system is based on the cell type (lymphocyte or reticulocyte), the degree of differentiation (undifferentiated or differentiated), and the pattern of the disease within the node (follicular or diffuse). This is shown in Table II.

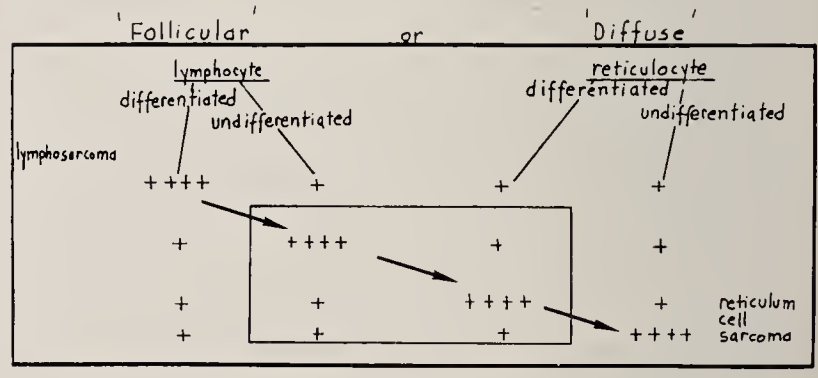

Table II[2]

This classification has several benefits to the clinician.

(a) It avoids confusion by giving previous 'borderline' cases a place on the spectrum and permits a reasonable estimate of prognosis. The major area of borderline cases falls within the central box, and can now be assessed.

(b) The prognosis is:

(i) improved by lymphocytes, well differentiated cells and a follicular pattern.

(ii) reduced by the association of lymphocyte depletion, undifferentiated cells, and a diffuse pattern.

(c) The transition of disease from benign to malignant is indicated by the arrows.

In 1950 Peters brought out the first method of clinical staging, and applied it to Hodgkin's disease. It would seem on first glance that such a staging method should be adaptable to other lymphomas, but it has not. This inability points up a very important feature of the other lymphomas — they frequently present with extranodal involvement. To overcome this lack, Peters has just recently devised a classification of lymphomas with "extranodal presentation". It is based on a ten year retrospective study of patients followed at the Princess Margaret Hospital. This unpublished method, shown in Table 3, is now ready for trial in a prospective study. Below it is a new classification of lymphomas by "lymph node presentation."

TABLE III[6]

CLINICAL CLASSIFICATION OF LYMPHOMAS BY "EXTRANODAL PRESENTATIONS"

I Disease in extranodal site alone *or* with involvement of one contiguous group or chain of lymph nodes.

II Disease in a single extranodal site with involvement of two adjacent lymph node chains.

III (a) Disease in single extranodal site and involvement of lymph nodes beyond stage II *without* extension to other side of diaphragm.

(b) Disease in two extranodal sites of different tissue origin.

(c) Disease in multiple extranodal sites in the same tissue of origin - (b) and (c) *without* lymph node involvement.

IV Extension of disease beyond stage III.

CLINICAL CLASSIFICATION OF LYMPHOMAS BY "LYMPH NODE PRESENTATION"

I Disease limited to one anatomical region or to two contiguous anatomical regions, on the same side of the diaphragm.

II Disease in more than two anatomical regions or in two non-contiguous regions on the same side of the diaphragm.

III Disease on both sides of the diaphragm, but limited to involvement of the lymph nodes and spleen.

IV Any lymph node region with involvement of liver, lung or bone marrow (excluding chronic lymphatic leukemia).

In Hodgkin's disease divide each stage into:
(a) without systemic effects of disease
(b) with systemic effects of disease.

Thus, the classification of lymphomas and the assessment of patients is soon to be based on more than just the histological criteria, for the advantages of clinical staging parallel and complement the histology.

THE EVOLUTION OF THE CLASSIFICATION OF HODGKIN'S DISEASE

Since its description in 1832 there has been almost continuous controversy over the etiology of Hodgkin's disease. To the early histologists the cellular pleomorphism was quite distinct, and suggested an inflammatory reaction. Sternberg (1898) attributed Hodgkin's disease to tuberculosis, but Reed (1902) decided the association with tuberculosis was coincidental, and concluded that the disease was of inflammatory origin. Since then various viruses and rickettsia have been incriminated. The term 'reticulosis' was introduced in 1938, but did not receive its present meaning until Lumb redefined it as "indicating the reaction to varying stimuli of those mesenchymal cells large numbers of which persist into adult life in an immature form capable of multipotential differentiation". In this sense reticulosis has the same shade of meaning as fibrosis or gliosis, and thus many stimuli could be operative to produce neoplasm.

The pains of classifying Hodgkin's disease have gone through many of the same stages as the lymphomas. The Jackson and Parker attempt lumped 80% of cases into one group, and stood as the major criterion until the system of clinical staging first appeared in 1950. Then, more recently a spectrum of Hodgkin's disease has been presented by Lukes (1966). Before presenting these classifications a brief review of the pathological features of Hodgkin's Disease will be presented.

Microscopic Pathology — Hodgkin's disease is a tumor of mixed cell differentiation (e.g. lymphocytes and reticulum cells) which has as its most important component large, pale-staining, abnormal reticulum cells which have two or more 'mirror image' dark-staining nuclei and prominent nucleoli. Without these cells the diagnosis of Hodgkin's disease cannot be made. Further significant associated features are cellular pleomorphism consisting of neutrophils, eosinophils, plasma cells, fibrosis and necrosis. In modern thinking the abnormal reticulum cells (Reed-Sternberg) are considered to be the malignant element, and the other cells of a reactive nature.

Gross Pathology — The nodes tend to be slightly firm due to the fibrosis and become matted when penetration of the capsule occurs. Cut section reveals a uniformly gray, translucent, moist homogeneous appearance (fish flesh) with yellow patches of necrosis scattered intermittently. The spleen is enlarged and its cut surface shows "suet-like" deposits of Hodgkin's tissue scattered throughout.

JACKSON AND PARKER CLASSIFICATION

In 1944 Jackson and Parker published a classic series on Hodgkin's disease. They attempted to show the influence of histology on the prognosis of the disease. From what was then known as Hodgkin's disease (Hodgkin's Granuloma) they separated off two subgroups: Hodgkin's Paragranuloma, and Hodgkin's Sarcoma.

Paragranuloma — Superficially this resembles Hodgkin's Granuloma, but usually pursues a more benign course. The histologic pattern is predominated by lymphocytes without obliteration of the architecture, and a few widely scattered Reed-Sternberg cells. Reticulum cells, a few eosinophils and plasma cells complete the picture. Necrosis and fibrosis are conspicuous by their absence.

Granuloma — Abundant fibroblasts and reticulin are heavily laden with neutrophils, lymphocytes, plasma cells, eosinophils and many Reed-Sternberg cells. Necrotic areas are common, being surrounded by reticulum cells and in-growing fibroblasts.

Sarcoma — This tumor histologically resembles reticulum cell sarcoma but it differs by the presence of abundant diagnostic Reed-Sternberg cells.

The Jackson and Parker classification did have some value, but it had a major drawback in that 80% of patients with Hodgkin's were placed into the 'granuloma' category, and within this category there were widely varying survival rates. The granuloma variety was too heterogeneous to merit its continued use.

CLINICAL STAGING:

The frustration of an inaccurate histological approach to Hodgkin's led to search in other parameters of the disease. Clinical staging based on the extent of the disease became popular in about 1950. A revised method by Rosenberg is shown in Mr. Puley's article on page 213.

TABLE IV

OLD STAGING CRITERIA OF HODGKIN'S DISEASE

Stage	*Features*
I	Involvement of a single site or lymphatic region.
II	Involvement of two or three proximal lymphatic regions
	A. with no symptoms of generalized disease.
	B. with symptoms of generalized disease.
III	Involvement of two or three distant lymphatic regions.

Constitutional symptoms are found to worsen the prognosis, and those considered are pruritis, fever, night sweats, and a weight loss of 10% or more.

In an excellent review of Hodgkin's disease in the N.E.J.M. in 1964, Aisenberg reaches the conclusion that clinical staging has more practical clinical significance than Jackson and Parker's histological classification. The clinical staging shown above was helpful, but fell down in one very significant area — that of midline abdominal masses which could not be distinguished as retroperitoneal or 'extranodal' disease. Thus stage III became a wastebasket for disease beyond stage II.

The development of lymphography and its application to the lower limb to show lymph vessels and glands in the femoral, inguinal, iliac and para-aortic chains made possible a separation of stage III into stage III and IV, (see article on lymphography).

At present, clinical staging is considered on an equal basis with the reported histology in establishing the potential curability and the progression of the disease.

LUKES CLASSIFICATION

In recent years the accuracy of histological identification and improved clinical assessment have occured simultaneously. Robert J. Lukes in 1966 published a study on 377 U.S.A.F. servicemen in which he revised Jackson and Parker's classification and produced six subclassifications which permit a more informative histological grading. The evolution from Jackson and Parker's classication is shown as follows:

TABLE V

Median survival (yr.)	*% Distribution*	*Jackson & Parker*	*Lukes*	*% Distribution*	*Median survival (yr.)*
11.2	8%	Paragranuloma (a) (b)	(a) L & H Diffuse	6.1%	12.4
			(b) L & H Nodular	10.6%	7.4
3.2	91%	Granuloma (b) (c) (d) (e) (f)	(c) Nodular Sclerosis	39.3%	4.2
			(d) Mixed	25.7%	2.5
			(e) Diffuse Fibrosis	12.4%	0.9
0.6	1%	Sarcoma (f)	(f) Reticular	5.6%	2.3

The primary feature of Lukes classification is the division according to the degree of lymphocyte predominance or depletion. Generally he noted:

1. *Inverse relationship between the frequency of lymphocytes and Reed-Sternberg cells:*
   (a) Lymphocyte proliferation is associated with few Reed-Sternberg cells (L & H i.e. lymphocyte and histiocyte types).
   (b) Lymphocytic depletion is associated with a high proportion of Reed-Sternberg cells (Diffuse fibrosis and Reticular).
2. *Connective tissue is observed in two forms:*
   (a) Orderly distribution of interconnecting bands of collagen (Nodular Sclerosis).
   (b) Irregular distribution of finely fibrillar reticular connective tissue (Diffuse Fibrosis).

HISTOLOGICAL FEATURES OF LUKES CLASSIFICATION

I Lymphocyte Proliferation

—lymphocyte proliferation with histiocytes of reactive character which have abundant pale, eosinophilic cyto-

plasm, medium sized nuclei with delicate uniformly distributed chromatin and small eosinophilic nuclei.

(a) *L & H Diffuse:*

Well differentiated lymphocytes or histiocytes in any proportion, eosinophils and plasma cells are present. There is essentially no fibrosis and necrosis is absent. Classic R-S cells are few but large polypoid cells related to R-S cells may be frequent. The cellular proliferation extends throughout the lymph node and obliterates the sinusoids by compression.

(b) *L & H Nodular:*

This group ressembles the diffuse, but has a nodular pattern. In general, nodular lesions have lymphocytic predominance, but histiocytes are more common in diffuse lesions. The nodules, best demonstrated by reticulin stains, are often present only in a portion of the node.

II Nodular Sclerosis

This is a regional expression of Hodgkin's disease in the mediastinum. Histologically it consists of interconnecting bands of collagenous connective tissue circumscribing nodules of abnormal lymphoid tissue which contain various large mutilobular R-S cells. The associated cellular proliferation may be primarily lymphocytic or of fixed composition.

III Mixed Type

Of variable composition, this occupies a mid-position between lymphocyte abundance and depletion. The wide spectrum of cells is present throughout the node with a moderate degree of disorganized fibrosis without collagen formation. The typical R-S cells are quite numerous and prominent. This type most closely fits the 'granuloma' type of Jackson and Parker.

IV Lymphocyte Depletion

(a) *Diffuse Fibrosis* — a disorderly picture of fibrosis without collagen band formation and primarily representative of lymphocyte depletion. This type is often seen as the end result of terminal untreated Hodgkin's and in post therapy autopsy findings.

(b) *Reticular.* The R-S cell is the predominant component in this process which may have a mixed cellular composition as well as or only pleomorphic and sarcomatous R-S cells.

The following schematic representation of variation in the morphologic features in the histologic types of Hodgkin's brings the above information into an easier perspective.

TABLE VI[3]

Histologic groups	*lymphocyte*	*histiocyte*	*eosinophil*	*plasma cell*	*fibril reticulin*	*collagen*	*R-S cells*
L&H Nodular	+++++++	+	0	0	0	0	+
L&H Diffuse	++++++	+++	0	0	0	0	+
Nodular Sclerosis	+-++++	+-++	+	+	+	+-++++	+
Mixed	+	+++	++	+	++	0	++
Diffuse Fibrosis	0	+	+	+	++++	0	++
Reticular	+	0	++	+	+	0	+++++

The advantage of the Lukes' classification can only be realized if it subdivides the 'granuloma' group of Jackson and Parker, and provides a better prognostic tool for the clinician. Indeed it does this, as can be readily seen by comparison of distribution of Hodgkin's in the two classifications. Further, Lukes found a good correlation between lymphocyte proliferation and clinical stage I disease, and also between lymphocyte depletion and clinical stage III disease[3].

IMMUNOLOGIC CONSIDERATIONS OF HODGKIN'S DISEASE

Amidst the frustration and seeming ineptness at determining the etiology of Hodgkin's disease, there is appearing a tremendous amount of data and information relating to the immunological abnormalities of this disease. By way of recapitulation, when we considered the lymphomas we noted that poorer prognosis was associated with a lymphocyte depletion. In lymphomas excluding Hodgkin's this occurs terminally, but in Hodgkin's clinical abnormalities appear earlier and usually remain, only to get more severe terminally. In Lukes' classification the abnormalities are associated with lymphocyte depletion and active disease is seen in Diffuse Fibrosis and Reticular disease.

Infections:

Patients with Hodgkin's have a high predisposition to tuberculosis, cryptococcus and Herpes Zoster infections. The significance of the immunologic defect came only when it was recognized that patients with Hodgkin's had

a high incidence of tuberculin negativity, even with overt tuberculosis. This was pointed out by Schier and co-workers to be an anergy (underreactivity) to all allergens that elicit the delayed type sensitivity. Cutaneous anergy has been documented in leukemia and carcinoma, but it differs from the anergy of Hodgkin's in appearing late. The reason for the anergy has also been likened to the loss of tuberculin sensitivity in children with measles or exanthemata. The practical application of this defect is often very perplexing to the clinician, because with progression of the disease infection becomes a very important factor, and with complaints of pain, fever, etc., one cannot distinguish between active progressive disease and infection without a complete re-assessment. Many patients suspected of having 'progressive' disease have died in reality from infections.

Homograft Rejection:

This phenomenon also involves a delayed type hypersensitivity, and bears a relation to thymic disease in animals. It has been found that many patients with Hodgkin's demonstrated impaired homograft rejection. Also, the prolonged survival of bone marrow grafts has been observed in patients with Hodgkin's.

Antibody:

The antibody formation in response to many tested antigens (eg. brucella, pneumococcus, tetanus) has usually been found to be quite well preserved until the terminal stages of the disease. This property is consistent with the normal or slightly elevated gamma globulin found in patients with Hodgkin's. In this feature, Hodgkin's forms a striking contrast with chronic lymphatic leukemia and other forms of hypogammaglobulinemia and agammaglobulinemia, in which there is characteristically a depressed gamma globulin formation and resultant infection.

AN IMMUNOLOGICAL CLASSIFICATION OF HODGKIN'S DISEASE

The interest in Hodgkin's disease has led to great expense for experimentation on the immune mechanism and its correlation with clinical Hodgkin's. Sokal (Rosewell Park) and Aisenberg (Massachusetts General Hospital) have done much to assess the immune mechanism and its competence, especially with respect to Hodgkin's. The main defects uncovered have been with respect to cellular immunity rather than humoral immunity. Sokal has recognized the sequence in which loss of immunological competence occurs, and has correlated this with reproducible clinical findings — thus providing another aid to the assessment and 'prognostic index' of Hodgkin's. The sequence is outlined as follows:

TABLE VII[5]

PROGRESSION OF IMMUNOLOGICAL DEFICIENCY IN HODGKIN'S DISEASE

Before Diagnosis

Pre-existent delayed skin test responses diminished or lost.

Very high incidence of skin test anergy; only the strongest responses remain.

Loss of skin sensitization to dinitrochlorobenzene.

BCG vaccination induces positive tuberculin reaction, except during active disease with moderately severe systemic manifestations.

Delayed skin test anergy even during remissions. Susceptible to H. Zoster, but eruption remains localized. Some loss of antibody response to primary immunization.

Increased susceptibility to fungal infections and tuberculosis. Tuberculin positive during active tuberculosis, or after high doses of BCG.

H. Zoster disseminates. Antibody production impaired, but is usually adequate for protection against disease. Delayed rejection of homolgous skin grafts.

Terminal Disease

Tuberculin negative even during active TB. Death may be caused by fungal infection. Homologous skin graft not rejected. Antibody production severely impaired, but resistance to many agents remains until death.

It is readily realized that this approach to Hodgkin's is clinically of value in assessing disturbed function (ie. cellular immunity). It is entirely conceivable that in the future, the injection of antigens which produce a delayed hypersensitivity (ie. cellular) response will assume an important role in patient assessment, management, and prognosis.

CONCLUSION

This paper has attempted to enlighten the reader, particularly the confused student, with regard to the evolution and current status of the pathological and clinical concepts of the various lymphomatous disorders. A clear understanding of this serious spectrum of diseases is important in that they represent a continued challenge to the diagnostic and therapeutic acumen of the conscientious modern day physician.

ACKNOWLEDGEMENT

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The Investigation Of Hodgkin's Disease

R. J. Puley 6T8

INTRODUCTION

In 1832 Thomas Hodgkin published a paper in the "Transactions of the Medical and Chirurgical Society of London" entitled "On Some Morbid Appearances of the Absorbent Glands and Spleen". His paper was the first clear account of disease originating in the lymphoreticular system and his name became attached to this particular disorder. Hodgkin's disease has been a point of controversy now for over one hundred years; many pathologists have considered it to be an infectious granuloma, incriminating several organisms including the tubercle bacillus (human and avian), diphtheroid bacillus, Brucella organisms and various viruses. Today Hodgkin's disease is generally recognized, both clinically and histologically, as a progressive lymphoreticular neoplasm allied to other tumors of the lymphoreticular system. Because of progress in treatment utilizing surgical excision, irradiation, and chemotherapy, Hodgkin's disease is now potentially curable. It is therefore mandatory that an organized plan of investigation be instituted for each patient to confirm the diagnosis, to indicate the most suitable therapeutic regimen, and to determine the prognosis. Such an investigation should include a complete history and physical examination, biopsy, routine tests and special investigative procedures.

HISTORY AND PHYSICAL EXAMINATION

From a detailed history and physical examination a presumptive diagnosis of Hodgkin's disease can be made. Characteristically the patient gives a history of excellent health before the onset which usually is manifested by adenopathy with or without systemic symptoms. Occasionally a brief antecedent history of upper respiratory tract infection or of infection about the head and neck (eg. tonsillitis) is given. Hodgkin's disease has a characteristic bimodal age distribution with the first mode between fifteen and thirty-four years and the second mode at over fifty years of age. Males are more frequently affected than females. The most common presenting symptoms are those of painless progressive enlargement of a superficial lymph node or a group of lymph nodes, especially in the neck, and various systemic manifestations including fever (infrequently Pel-Ebstein), night sweats, pruritus, weight loss, malaise, anorexia, nausea and vomiting, and alcohol pain. The nodes are discrete and moveable at first; later they become matted together and fixed. If they develop rapidly or infiltrate nerves they may become tender.

The mode of onset of Hodgkin's disease may vary greatly however. Axillary, inguinal, mediastinal and retroperitoneal para-aortic nodes may be the first sites of lymphadenopathy. Extranodal primary sites include tonsils, nasopharynx, thymus, thyroid, stomach, rectum, liver, spleen, heart and pericardium, genitourinary tract, bones and central nervous system. Manifestations of mediastinal involvement include dyspnea, brassy cough, dysphagia and obstruction of the superior vena cava. The mediastinal node compression may mimic other tumors and infections of the chest. Pulmonary lesions include pulmonary fibrosis, cavitation, endobronchial lesions and pleural effusion. Abdominal and retroperitoneal disease may cause bleeding, obstruction, nausea, vomiting and diarrhea secondary to infiltration of the mucosa of the gastrointestinal tract or mesenteric lymphatic obstruction and intestinal lymphedema. Liver involvement may become manifest firstly by jaundice secondary to fibrosis of the portal triads or obstruction by nodes at the porta hepatis or secondly, by the stigmata of portal hypertension. Pressure symptoms from a large mass in the retroperitoneum or from enlargement of liver or spleen are common. Hematuria, pyuria, chyluria or pain is found when the genitourinary tract is involved. Localized pain and tenderness, spontaneous fractures and areas of rarefaction or sclerosis on roentgenograms are the most common manifestations of bone involvement. By extension from the adjacent lymph nodes via the intervertebral foramina, the tumor may infiltrate the epidural space producing neurological signs. Less commonly brain and spinal cord may be directly involved giving cranial nerve palsies. Peripheral neuropathies and involvement of the eye with invasion of lacrimal gland, uveal tract, optic nerve or retro-orbital space are other manifestations of neurological involvement. Cutaneous manifestations include excoriations produced in response to pruritus, direct infiltration by the specific tumor cells, 'id' reactions, brownish skin pigmentation and herpes zoster.

As well as providing suggestive evidence of occult sites of disease, the detailed history and physical examination will also yield important information regarding prognosis. Prognostically poor signs include systemic manifestations, short prediagnostic history suggestive of aggressive disease and poor response to initial therapeutic procedures. The disease usually progresses more rapidly in older patients and in males.

Before biopsy an attempt should be made to exclude other causes of lymph node enlargement. Lymphadenopathy is seen in acute regional and systemic infections (streptococcus, staphylococcus, plague, infectious mononucleosis, cat scratch disease, lymphogranuloma venereum), chronic infections (tuberculosis, syphilis, fungus infections), sarcoidosis, congenital abnormalities (lymphangiomas), allergic reactions (serum sickness), leukemia, other lymphomas, and metastases from non-lymphomatous malignant disease.

BIOPSY AND PATHOLOGY

Therapy for Hodgkin's disease should not be undertaken without histologic confirmation of the diagnosis.

In addition a histologic grading such as that suggested by Lukes and Butler is informative regarding clinical staging and prognosis.

No more than three to four weeks should elapse between recognition of unexplained lymph node enlargement and a diagnostic biopsy. The pathological features are most easily recognized from large cervical lymph nodes. If the pathologist is uncertain, another biopsy of an adjacent lymph node often gives the answer. Biopsy of inguinal lymph nodes should be avoided if possible, particularly in men, because the interpretation may be made difficult by previous chronic infectious processes. If disease is confined to deep lymph nodes in the thoracic or retroperitoneal region a scalene lymph node biopsy, thoracotomy or laparotomy may have to be considered. If biopsy of femoral, inguinal, iliac or retroperitoneal lymph nodes is contemplated, it is advisable to perform this before lymphography, as a nonspecific inflammatory reaction to Ethiodol may obscure in part the histology of the lymph node.

In 1966 Lukes and Butler revised Jackson and Parker's original classification of Hodgkin's disease and produced subclassifications permitting a more informative histologic grading. The reader is referred to Mr. Flett's article in this issue for a detailed description of these classifications.

The association of histologic grading, clinical staging and prognosis implicated by the studies of Lukes and Butler can be summarized as follows:

(1) Predominance of lymphocytes or histiocytes or both in tissues involved by Hodgkin's disease is associated with clinical stage I disease and the most favourable prognosis, and is classified as "Lymphocytic" or "Histiocytic" respectively.

(2) The group of cases classified as "Nodular Sclerosis" is also associated with a relatively long survival and this form of the disease is usually found in the mediastinum and adjacent lymph nodes.

(3) Depletion of lymphocytes, whether accompanied by "Diffuse Fibrosis" or by a proliferation of Reed-Sternberg cells and abnormal reticulum cells as in the "Reticular" form of the disease, is associated with clinical stage III or IV disease and the least favourable prognosis.

ROUTINE INVESTIGATION

Accompanying adequate history, physical examination, and biopsy complete with histologic report, certain diagnostic tests are essential in most patients.

1. Hemogram

Anemia is a frequent complication. A few patients have a hypochromic microcytic anemia, usually secondary to blood loss. Eighty percent of patients with late Hodgkin's disease develop a hemolytic anemia characterized by normochromic, normocytic RBC's, anisocytosis, spherocytosis with increased RBC fragility, reticulocytosis, minimal icterus and a negative direct Coombs test. Correlation between the severity of the anemia and progression of the disease is often possible.

The leukocyte changes are inconstant and not diagnostic. Leukocytosis with neutrophilia occurs in more than fifty percent of patients. An absolute increase in the number of lymphocytes suggests some disease other than Hodgkin's.

Platelets are normal or increased in number early in the illness; with progression they usually diminish in number because of cumulative toxic effects of radiation and chemotherapy and more rarely because of bone marrow replacement by Hodgkin's tissue.

The ESR, a good index of activity, increases in the presence of active disease and falls after effective therapy or during spontaneous remission.

2. Urinalysis and Renal Function Tests

Urinalysis may reveal chyluria. Retroperitoneal nodes may obstruct the ureter causing hydronephrosis and an elevated BUN.

3. Liver Function Tests

An elevated serum alkaline phosphatase in the absence of bony involvement and a normal serum bilirubin is very suggestive of liver parenchymal involvement. If the bilirubin is elevated as well, portal lymphadenopathy may be present causing biliary duct obstruction.

4. Serum Proteins

Serum albumin is often reduced due to decreased synthesis or malabsorption. Serum α_1 globulin (77% cases) and β_2 globulin (35% cases) often are elevated. γ globulin is decreased in almost half, elevated in 46%.

5. Radiographs

PA and lateral views of the chest are done routinely and tomograms done if the routine films demonstrate hilar or other involvement. Gastrointestinal radiographic examination is important to detect evidence of extrinsic pressure from lymph nodes or an enlarged organ or to investigate malabsorption. Skeletal radiographs including at least thoracolumbar spine and pelvis are indicated. Sclerotic vertebrae ("ivory vertebrae") may be seen, but most lesions are lytic. The popularity of the IVP to detect enlarged nodes displacing the ureters is fading because lymphography produces similar but much more accurate information.

SPECIAL INVESTIGATION

The advent of specialized investigative procedures has permitted the identification of disease in occult areas and given new meaning to a clinical stage described as limited to one anatomic region. It should be emphasized that not all these tests are necessary in every patient.

1. Lymphography

This technique, which visualizes the lymph vessels and nodes by filling them with a radiopaque substance allows recognition of involvement of iliac and para-aortic nodes before the remote disease causes symptoms or clinically detectable signs. If irradiation is to be used, lymphography can help to define better the area to be treated. It also offers a measure of response to therapy, and may be helpful in explaining certain obscure clinical findings, such as lymphedema of the lower extremities in the absence of inguinal lymphadenopathy.

2. Isotope Scanning

Liver and spleen scanning are now routine. Heat-treated RBCs incubated with radioactive chromium and injected intravenously show the normal spleen, its size and position, and any enlargement due to disease. Splenic function can be assessed by estimating the blood clearance time for these denatured RBCs and also by measuring their rate of uptake in the spleen. Liver scans with radioactive gold or technetium -99- sulphur colloid demonstrate hepatomegaly or else patchy areas of neoplastic infiltration. The technique of scanning nodes in the mediastinum is not yet satisfactory, although improving.

3. Bone Marrow Examination

This procedure is helpful when a peripheral blood film has shown abnormal cells or when there is evidence of skeletal disease.

4. Multiple Biopsies

When the investigator's suspicions are aroused by atypical features in the progression of the disease another lymph node should be biopsied. Multiple biopsies early in the disease improve diagnostic accuracy.

5. Diagnostic Taps

(a) Lumbar puncture may be used to determine meningeal involvement.

(b) Thoracocentesis and paracentesis may be used to diagnose chylothorax or chylous ascites.

(c) Pericardial taps are used to discover the source of pericardial effusion.

6. Cytologic Studies of sputum, bronchial washings, and urine sediment may reveal tumour cells characteristic of Hodgkin's disease.

When these investigative procedures disclose extranodal involvement, the disease is far advanced and palliation is the only resource. However, when this stage is recognized earlier, more prolonged remissions are obtained by suitable therapy. Improvement in therapeutic results awaits earlier and more accurate definition of the extent of the disease.

CLINICAL STAGING

Once the above investigative procedures have been completed the geographic extent of the disease can be fully appreciated. It is now possible to attach a clinical stage to each patient. Up to the present a three stage classification has been used; the revised method of Rosenberg utilizing four clinical stages is outlined below.

HODGKIN'S DISEASE — PROPOSED NEW STAGING CRITERIA

Stage	*Revised clinical classification*
I	Disease limited to one anatomical region or to two contiguous anatomical regions, on the same side of the diaphragm.
II	Disease in more than two contiguous regions or in two non-contiguous regions on the same side of the diaphragm.
III	Disease on both sides of the diaphragm, but limited to involvement of the lymph nodes, spleen and Waldeyer's ring.
IV	Involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract or any tissue or organ other than the lymph nodes, spleen or Waldeyer's ring.

Each stage is subdivided into two categories:

A. without systemic effects of the disease,

B. with systemic effects of the disease.

This staging approach is useful in suggesting prognosis.

Finally, clinical staging provides a basis for comparison of the clinical experiences of different treatment centres. Constant evaluation of current management is needed to presage a more effective therapeutic programme in the future.

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The Management of Hodgkin's Disease

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INTRODUCTION

The treatment of Hodgkin's disease, and particularly the correct interpretation of the results of treatment, depends on the adequacy of the initial investigations. The new histologic classification of Hodgkin's disease, as proposed by Lukes, has been outlined elsewhere in this issue, along with the prognostic significance of the six types. Even more important to the clinical management of the condition is accurate staging, for the stage of disease indicates the progress of the condition, and its extent when therapy is undertaken. It is therefore, an index of the magnitude of the clinical problem. The newer methods of establishing with accuracy the stage of disease have also been outlined elsewhere in this issue. Without the use of lymphography, chest x-ray, skeletal survey, and in some cases, vena cavography and mediastinal tomography to supplement the thorough history and physical examination and conventional laboratory tests, the staging of Hodgkin's disease is at best inaccurate, and often meaningless and misleading.[1]

The complexity of the treatment of this condition is such that it should only be undertaken in a large centre, where radiotherapist and internist, each with special experience in this field, can cooperate to achieve best results. High cure rates have only been reported from centres with very sophisticated radiotherapeutic equipment.

GOALS OF TREATMENT

1. Cure

This is ultimately the goal in all cases. At present, it is most reasonable to strive for cure in:[2]

(a) young patients in general. The prognosis in Hodgkin's disease is much better under the age of fifty years, than over this age.

(b) stage I and II disease, and in young people with stage IIIA disease.

2. Palliation

This is possible even in advanced disease, though it does not necessarily prolong life. In addition to the three main methods to be described, medical management of certain additional features of the disease may prolong life. Infections must be treated vigorously; anemia may require transfusions; psychological support is very important.

TYPES OF TREATMENT AND THEIR SCOPE IN THE MANAGEMENT OF HODGKIN'S DISEASE

1. Surgery

Although there have been reports of long-term survivals following radical lymph node dissection in patients with well localized Hodgkin's disease, surgery seems to have no advantage over judiciously administered radiotherapy in such cases.[3] In more wide-spread disease, radiotherapy is unquestionably superior to surgery, in its overall efficacy.

However, surgery does have several adjunctive uses in management.

(a) Biopsy for diagnosis is certainly the most frequent application of surgery in this field.

(b) Surgery may play a part in the treatment of problems associated with Hodgkin's disease, such as infection, to which these patients are so prone.

(c) Surgical splenectomy may be used to treat the secondary hypersplenism of Hodgkin's disease. This is not as well established as the role of surgery in primary hypersplenism. Secondary hypersplenism occurs late in the course of Hodgkin's disease, and its surgical treatment benefits only a few patients. Splenectomy has been performed for anemia when the Coombs' test is negative and there are no abnormal serum globulins, to obviate the need for repeated transfusions. It may be indicated when leukopenia and/or thrombocytopenia prevent further radiotherapy or chemotherapy.

Because hypersplenism is such a late event in the natural history of this disease, the patients are often very ill pre-operatively, and in a series of twenty patients, seven (35 per cent) died within thirty days of surgery. The other thirteen patients were variably improved with regard to their need for subsequent transfusions, and with regard to their cytopenias.

2. Radiotherapy

Hodgkin's disease is now a *curable* condition, with the use of radiation therapy.[4] While recurrence of disease in previously treated fields was once common, it is virtually zero with new megavoltage equipment, applying 3500-4000 rads over 4 weeks to appropriate areas. The accompanying graph (Fig. 1) shows that an adequate dose of radiation is essential for a consistent tumoricidal effect.

The impressive long-term survival figures reported by various workers, including Gilbert, Peters, and several others, all were obtained with high-dose, wide-field radiotherapy.

Megavoltage X-ray, and gamma-beams from linear accelerators, betatrons, and Co^{60} units permit delivery of these effective tumour dose levels with little skin reaction. The lateral scatter of these new beams is minimal; for example, the para-aortic nodes may be irradiated with little danger of radiation nephritis.

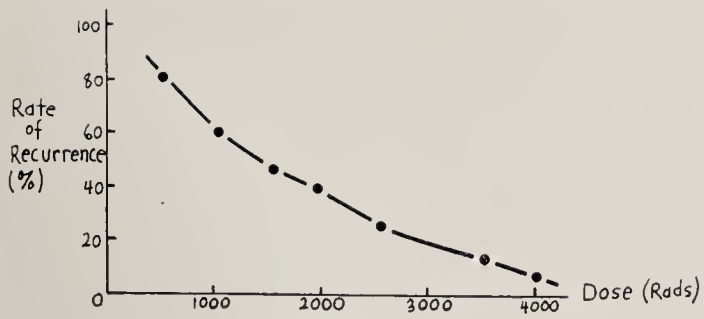

FIG. 1

There may be a leukopenia and thrombocytopenia associated with treatment, especially if wide fields are involved, but this usually reverts to normal within weeks or months. Radiation to the mediastinum is frequently accompanied by temporary dysphagia due to oesophagitis, and cough for several months due to radiation pneumonitis. The exaggeration of the pulmonary vascular markings found in this latter condition usually clears promptly, leaving a normal radiograph, and little or no functional impairment. Fatigue is commonly a prominent symptom during any extensive course of radiotherapy, but subsides once treatments are completed.

Lymphography and inferior vena cavography have revealed that stage III and IV disease is more common than was thought, and may comprise 35 to 50% of all cases of Hodgkin's disease. The fact that megavoltage radiotherapy can be carried safely to high dose levels over the very extensive fields required by stage III and IV cases, is therefore of great importance. In a recent series, involving treatment of stage III and IV Hodgkin's disease, there were no major hematologic complications, though a very large fraction of the active bone marrow of the body was treated. The W.B.C.'s usually remained about 2000-3000, and the platelet count usually remained above 100,000.

It has been shown by new investigative techniques, in particular mediastinal tomography, lymphography, and inferior vena cavography, that Hodgkin's disease does not spread randomly, as some have suggested, but follows lymphatic pathways to contiguous areas.[4] Formerly, certain areas seemed to be "skipped", because the techniques to demonstrate their involvement were inadequate. Thus, more rational treatment plans may be formed, which involve giving radiotherapy to areas adjacent to known areas of involvement. Dr. Vera Peters has presented long-term survival figures for a series of patients treated with and without extended fields, which strongly suggest that the extended-field technique may improve survival.

There is now considerable evidence that long-term survivors, without evidence of active disease, are in fact cured of their Hodgkin's disease after an initial course of therapy. In a number of patients who have died of intercurrent disease several years after treatment, no evidence of Hodgkin's disease was detectable at postmortem examination. Also, it has been shown that those patients who develop a recurrence of disease after initial treatment usually do so within 2 years. The probability of new disease becoming evident after 5 years disease-free is almost certainly less than 5%. Recently however, several recurrences have been seen at the Princess Margaret Hospital in patients who had been disease-free for over ten years.

3. Chemotherapy

The indications for chemotherapy in Hodgkin's disease are:[5]

(a) For widespread disease with systemic manifestations. This is the principal use.

(b) In combination with radiotherapy, for localized disease.

(c) In acute situations, where rapid relief of signs and symptoms is necessary.

There are essentially 4 groups of drugs useful in this field:

(i) The alkylating agents.

(ii) The vinca (periwinkle) alkaloids.

(iii) Methylhydrazine compounds.

(iv) Adrenal corticosteroids.

The antimetabolites have been much less successful, and generally are not used.

This is a complex subject, and there are no definite rules to guide the selection of agent (or agents) or therapeutic plan. The systemic drugs do not have the destructive efficacy of locally administered radiation, and their use is secondary to a curative attempt by radiotherapy.

Because the dose schedules and details of administration are of interest only to the specialist in chemotherapy, we shall only mention the mechanisms of action of these drugs.

(i) Alkylating agents—damage cells by cross-linking with D.N.A.

(ii) Vinca Alkaloids—arrest cells in metaphase, in a manner similar to colchicine.

(iii) Methylhydrazine compounds — affect D.N.A. through the formation of intracellular peroxides.

(iv) Corticosteroids—are lympholytic.

It is not known whether these drugs act by inhibiting the growth of the neoplatic cells *per se*, or by suppressing certain functional activities of the abnormal cells, which induce cellular host reactions in the diseased nodes as well as causing systemic symptoms. These

chemotherapeutic agents may suppress the host reaction, and therefore the systemic manifestations of the disease, without seriously damaging the neoplastic process until such time as the disease itself progresses to a more resistant and malignant phase.

Used with radiotherapy to treat localized disease, chemotherapeutic agents may decrease the bulk of neoplastic tissue to be treated and may possibly enhance the action of the radiation.

Acute manifestations may be improved by drug therapy. For example, in spinal cord compression due to Hodgkin's disease, the salvage rate, in terms of recovery of neurologic function, was 73% in patients receiving nitrogen mustard and radiotherapy, but only 43% in those receiving radiotherapy alone.

In treating widespread systemic disease, 80 to 90% of patients in relatively good general condition will respond to their first course of therapy, and improvement following short interrupted courses may average 6 to 10 weeks. Slowly progressive disease is usually associated with a prolonged response to treatment, whereas transitory or partial improvement, despite adequate treatment, suggests a poor prognosis. When a refractory state to one drug develops, the others are usually less effective than formerly, but exceptions do exist.

Chemotherapy provides definite symptomatic relief in Hodgkin's disease, but there is still little evidence that it is responsible for significantly increased survivals. Radiotherapy still has the first priority in planning a therapeutic program for Hodgkin's disease. Only radiotherapy, of the methods available at present, offers good hope for cure of this disease.

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The Current Status Of The Lymphocyte - A Review Of Recent Thought

P. A. Jordan 6T8

For many years lymphocytes have been recognized as important in the immune mechanism. Let us first consider the immune response. The current thought is that there are probably two distinct varieties of the immune response. The *immediate phase* is characterized by the following:

1. A latent period for processing of the antigen, probably by the reticuloendothelial system or by neutrophils.

2. A proliferation of plasma cells and peripheral lymphocytes. These cells have a heavy basophilia that is due to the synthesis of RNA and protein and stain heavily with pyronin stains (pyroninophilic cells).

3. Enlargement of germinal centres and appearance of new follicles in lymph nodes, especially those adjacent to the antigenic stimulus.

4. Appearance in the serum of 19S, then 7S specific antibody.

5. The anamnestic response or immunological memory wherein a second exposure to an antigen effects an accelerated and augmented antibody response.

Delayed hypersensitivity is characterized by the following:

1. Proliferation of the RE system.

2. Local proliferation of lymphoid cells (lymphocytes and their transformed products) and production of a small amount of circulating antibody of questionable significance.

3. The passive transfer of this immunity requires lymphoid cells, or cell constituents.

Lymphocytes are important in the transplantation rejection phenomenon. It has been demonstrated by both Gowans and Hildemann that when small lymphocytes from adult mice are injected into genetically different, and therefore immunologically different, newborn mice, they are capable of causing a *graft versus host* reaction, the so-called "runting reaction" which ultimately results in the death of the host mouse.

In this reaction there is early decrease of thymus weight, associated with enlargement of the spleen and lymph nodes. The injected lymphocytes apparently direct their attack on the lymph nodes and spleen. The thymus acts either by providing thymocytes which become lymphocytes or by providing hormonal stimulation to the lymphoid tissue to proliferate. There is considerable recent evidence to support the latter mechanism. The

thymus finally atrophies and near the death of the animal the lymphoid tissue is exhausted and atrophies. It has been found that the injection of isogenic adult lymphocytes in the newborn period renders the animal tolerant and protects the recipient against such induced graft versus host disease.

Further, there is tolerance to homografts in the larval bullfrog in the presence of circulating large lymphocytes, but on the appearance of small lymphocytes, the animal is capable of a rejection reaction. Conversely, external drainage of thoracic duct lymph, (thus gradually depleting an animal of small lymphocytes) results in prolonged graft survival.

Lymphocytes (but not hyperimmune serum) from an animal sensitized to a graft are capable of passive transfer of sensitization to an indifferent animal. However, if the graft is placed in a millipore chamber, which prevents passage of cells but allows passage of non-cellular elements, thus isolating it from the hosts' lymphocytes, graft survival is permitted. Thus it may be concluded that contact of the sensitized cell and the sensitizing graft seems to be essential for rejection to occur.

It has been demonstrated that transferred sensitized lymphocytes distribute themselves throughout the host tissues, and transform into large pyroninophilic cells, but the cells which appear around the graft site are of host, not donor origin.

The host's cells are made capable of graft rejection even if the transferred sensitized cells are placed within a millipore chamber and cannot escape. This indicates the presence of some diffusable *"Transfer Factor"* which indeed has been extracted from sensitized lymphocytes and effectively confers sensitivity on an indifferent animal, even when injected in extremely small quantities.

It has been demonstrated that there are two distinct populations of small lymphocytes:

(a) A *long-lived* variety which probably survive about one year; these are probably involved in transplantation immunity and delayed hypersensitivity. Upon injection into other animals, these are unable to transfer the capacity to make serum antibodies unless the host is restimulated with antigen after injection of the lymphocytes.

(b) A *short-lived* population which are probably capable of the serum antibody response, and also are thought to be the cells which on stimulation become the large pyroninophilic and plasma cells which are the major producers of antibody.

On first encountering an antigen there is a *primary response* of the animal in which there is production of a large 19S macroglobulin probably by the large pyroninophilic cells which develop from lymphocytes. These are located in the cortical areas of the lymph nodes. This response can be effectively blocked by chronic thoracic duct drainage, a procedure which also depletes the lymph follicles of small lymphocytes. When lymph node cells in a millipore chamber are transplanted into a host animal, and the animal is stimulated antigenically, there is release of macroglobulin antibody into the chamber from the cells which transform into large blast-like pyroninophilic cells.

This transformation is identical to that seen in the cells of a lymph node draining the site of a skin homograft.

The second encounter of an animal with an antigen results in a *secondary response,* that is, production of a 7S gammaglobulin from the plasma cells and germinal centres of the lymphoid follicle. This reaction is not inhibited by chronic thoracic duct drainage.

Further evidence of the dichotomy of these two processes is available from the study of birds. In fowls, transplantation immunity and delayed hypersensitivity is controlled by the thymus, whereas humoral immediate antibody synthesis is controlled by the Bursa of Fabricius, a cloacal lymph organ. Removal of the bursa blocks the latter sequence, removal of the thymus the former. In rodents which normally are born before thymic development has reached a critical stage, neonatal thymectomy results in failure of peripheral lymphoid maturation and immunological incompetence manifested by prolonged survival of homografts. Grafting a thymectomized animal with a syngeneic thymus results in anatomic and immunological restoration of the peripheral lymphoid tissue and graft rejection mechanisms. This restoration occurs even if the thymus transplant is enclosed in a millipore diffusion chamber, implying a humoral regulatory mechanism.

Metcalfe has demonstrated *in vivo* and *in vitro* production by thymocytes of a *"lymphocytosis stimulating factor"* (LSF) which is a heat labile, filterable, non-diffusible substance. This LSF is present in increased amounts in patients with lymphoproliferative disorders. It is noteable that LSF has all the characteristics of a hormone; that is, it is produced by a ductless gland, carried in the plasma, acts on distant target cells, exerts a temporary effect which is under feedback control, and has activity which crosses species barriers.

The capabilities of the small lymphocyte have been investigated by various means with far reaching results. In tissue culture, peripheral small lymphocytes can be stimulated to transform into large blast-like cells, and divide — becoming protein producers at this time. They have been shown capable of producing IgG, IgA and IgM antibodies. Stimulation by phytohaemagglutinin (PHA), a mitotogenic crude extract of the kidney bean, causes the appearance of both specific antibody against antigen to which the cells had been previously sensitized, and of a non-specific gamma globulin. If however, the stimulation is by a specific antigen to which the cells had been previously sensitized, there is production of specific antibody only. In the latter process the transformation takes longer and a smaller proportion of cells are in-

volved; thus the stimulatory processes are probably different.

It can be demonstrated readily that when lymphocytes from two dissimilar individuals are mixed, cellular transformation and division occur. Thus, it was postulated that antigenic determinants on each person's lymphocytes stimulate the other's lymphocytes to proliferate and transform. This factor among others is used in matching tests for tissue histocompatibility. The *Mixed Lymphocyte Culture Test* is performed by such a procedure. An estimation, either by counting or by means of radioactive metabolic precursors, of the number of transformed cells, gives an indication of how strong will be the immunological reaction should tissue from the one individual be grafted to the other. A second test, the *Normal Lymphocyte Transfer Test,* utilizes the readily observed erythematous skin reaction seen in a person after the intradermal injection of normal living lymphocytes from the peripheral blood of another individual. These tests were described in the first issue of this volume of the Journal by P. Halloran.

This method, by quantitating the response, has led to quite accurate estimations of future graft survival time which have been borne out experimentally. A method currently in use entails the mixing of peripheral small lymphocytes of the prospective host and donor, incubating the mixture, then adding Trypan Blue and observing the uptake of this particulate dye by the cells. The amount of reaction between the two strains of cells can be quantitated, since normal lymphocytes take up extremely little Trypan Blue, whereas slightly damaged lymphocytes take it up readily. As the cells are stimulated antigenically they begin to damage the "graft cells" and by determining the uptake of dye, we may conclude that it varies inversely as the histocompatibility of two strains. A large uptake would lead one to suspect an early and destructive response on the part of the host against a graft, if this graft was transplanted.

Lymphocyte stimulation is presently being related to disease processes. For example, when tissue cultures of lymphocytes of patients with Hashimoto's Thyroiditis are exposed to thyroglobulin or PHA, they produce gamma globulin which appears to act as antibody toward thyroglobulin. Similarly, lymphocytes from patients with macroglobulinemia release macroglobulins into the culture medium upon stimulation; those from patients with multiple myeloma produce myeloma paraprotein, and even the 7S gamma globulin LATS can be shown to be produced in PHA-stimulated lymphocyte cultures from patients with Grave's disease. By similar testing, normal enlargement, but lack of gamma globulin synthesis, is seen using lymphocytes from patients with agammaglobulinemia.

The circulating lymphocytes in Hodgkin's disease are assumed to be immunologically deficient because the patients show poor responses in delayed hypersensitivity tests. The percentage of lymphocytes transformed morphologically after stimulation with PHA varied from less than 1% to 56% with respect to a normal control of 36-60%. This depression of response was correlated to some extent with the severity of the disease process, in some instances a low score being associated with total lymphopenia. The decreased response however did not appear to depend upon current or previous treatment; thus the deficiency appears to be a manifestation of the disease.

O'Brien discusses the role of lymphocytes in malignant disease. Apparently lymphocytes do not show chemotaxis toward bacteria, virus-infected cells or digested tissues but do show a special affinity to areas of cells undergoing mitosis. Any lymphocyte within 100 microns of a cell in telophase is attracted to it and moves across the cytoplasmic bridge connecting the daughter cells. The lymphocyte can be observed in a tissue culture chamber to penetrate the cell membrane of a malignant cell and move freely within the tumour cell (called emperipolesis). The question of whether this is in some way connected with the immune response represents a very important step in the future of malignancy control. On the other hand, perhaps these lymphocytes serve only a nutritional purpose for the malignant cells.

In recent years the concept of the role of the lymphocyte has changed radically. This paper has illustrated a few of the current thoughts regarding its role as an antibody producer, a plasma cell precursor, and an indispensible part of both immediate and delayed immune reactions. This field is rapidly opening up, and with tissue transplantation and malignancy control being two of the foremost frontiers, many new developments may be anticipated.

ACKNOWLEDGEMENT

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Lymphography: Radiographic Investigation Of The Lymphatic System

A. S. Gordon 6T8

ABSTRACT

In this paper, lymphography is discussed with respect to technique, application, interpretation, and indications. An evaluation of the relative merits, complications, and limitations is presented.

A. INTRODUCTION

"The most difficult aspect of lymphangiography lies not in mastery of the technique, but in the problems of interpretation . . . the information derived is subject to the inherent limitations of the examination, as well as the skill of the interpreter. Its usefulness depends to a large extent upon what is expected of the examination. It must be understood that it offers no panacea for absolute diagnoses but does represent the only non-excisional approach to the differential diagnosis of diseases of the lymphatic system."[1]

B. DEFINITIONS

Lymphography literally means the study of lymph vessels and lymph nodes; in the context of this article, however, the radiological study of the lymphatic system using a contrast material is implied. *Indirect* lymphography involves infusing contrast material from without into the lymph vessel, i.e. subcutaneously, intra-articularly, or per-orally. In *direct* lymphography, contrast material is injected directly into the lymphatic vessels, cysts, or lymph nodes.[6] Radiographs taken as the dye is being infused into the lymph vessels and thus showing contrast material within the lymph vessels comprise the *lymphangiogram*. The *lymphadenogram* is the series of radiographs taken more than 24 hours later. Here, the glands alone should contain the contrast material. The *lymphogram* is the adeno- and angiogram together. The contrast material is *Ethiodol* (Lipiodol), an ethyl ester of poppy seed containing 37% iodine. It is a fat-soluble, radiopaque substance.[2]

C. TYPES OF LYMPHOGRAPHY

Lower extremity lymphography is the most common. Dye is introduced into the dorsum of the foot. The lymphatics of the groin, external, internal, and common iliac, and para-aortic regions, and the thoracic duct are commonly visualized. Dye may be introduced into the *arm* and the axillary nodes seen. To demonstrate cervical nodes, the posterior triangle of the *neck* is used. Perirenal para-aortic nodes are rendered radiopaque by *spermatic cord* lymphography.

This article will deal mainly with lower extremity lymphography, but the other types will be mentioned where applicable.

D. ANATOMY OF THE NORMAL LYMPH NODE

A normal lymph node is either oval, kidney or spindle-shaped[6] and varies in size from 0.5 - 5.0 cm.[1] in length. As a general rule, the greater the number of nodes in an area, the smaller the size of the nodes. The reverse is also true.

The outer part of the node is the *cortex,* and the more loosely structured central part is termed the *medulla.* Connective tissue trabeculae course inwards from the connective tissue capsule. There is a subcapsular *marginal sinus* in the cortex into which the *afferent lymphatics* discharge. The latter enter the periphery of the node on the convex surface. Lymph flows from the marginal sinus, through the *sinusoids,* into the medulla, and exits at the *hilus* via the *efferent vessels.* The cortical *primary lymphoid follicles* are suspended between the trabeculae and may or may not have inner, *secondary* or *germinal follicles.* These follicles consist mainly of a fine reticular mesh packed with lymphocytes in keeping with a lymphogenic function. In the medulla, the collections of lymphocytes are now called the *medullary cords.* The sinusoids are adjacent to the vascular trabeculae. They have a coarser reticular mesh in which reticulo-endothelial cells are suspended, suggesting a filtration function.

E. FUNCTION OF LYMPH NODES

Lymph nodes are thought to have two main functions, namely filtration of particulate matter and the development of immune responses to such things as foreign protein, viruses, and bacteria. Many investigators have questioned the role of lymph nodes in the spread of cancer.

Are lymph nodes barriers which filter and kill malignant cells, or do they merely store such cells? Thus should axillary lymph nodes be prophylactically removed in carcinoma of the breast, or should they be removed only when involved, or should they be removed at all? If lymph nodes kill malignant cells, will irradiating the nodes alter the process favourably or unfavourably? Is there any way of increasing the malignocidal properties of lymph nodes? O'Brien[9] and Herman[7] offer two opposing views on these questions which

are of paramount importance in the practical management of any patient with a clinically localized malignancy.

The immunological properties of lymph nodes are too controversial and complex to be gone into here, except to state that nodes are responsible for production and storage of lymphocytes and plasma cells for the immune response. They are important memory banks. Kinmonth[16] has recently suggested that the para-aortic nodes are more responsible for the immunological response than other lymph nodes (see Recent Advances in this issue).

F. TECHNIQUE OF THE PROCEDURE[10 11]

A solution of Patent Blue 5 (a blue dye) and 2% lignocaine (a local anaesthetic) is injected into the interdigital web between the first and second toes bilaterally. For upper limb procedures, injection between the index and middle fingers is used. The patient is then taken to the O.R. and the field prepared as for a surgical procedure. Within 10 to 15 minutes, the superficial lymphatics become blue. Under local anaesthesia, a vertical 1½ cm. incision is made over a vessel usually just lateral to the extensor hallucis longus tendon at metatarsal level, about 3-4 cm. proximal to the site of injection. This blue lymphatic vessel is seen either before the incision has been made or during careful exploration of the incision. Blunt dissection frees the vessel which is then cannulated with a 27 gauge needle connected to a small bore polyethylene tube. A total dose of 0.25 ml/kg body weight of Ethiodol is injected at a rate of approximately 1 cc. per 12 minutes. This usually amounts to 6-10 cc. per foot. It is important to keep the amount of dye to a minimum to prevent complications.

Using a similar technique, a 30 gauge needle, and a smaller amount of dye, the lymphatic drainage of the upper limb (the axillary and periclavicular nodes) can be seen.[11]

The procedure must be monitored carefully. Ideally a fluoroscope should be used to follow flow abnormalities. If lymphatic obstruction is present to any great degree, the examination is curtailed. Otherwise, oil will enter the systemic venous circulation via lymphovenous communications and may cause severe pulmonary Ethiodol embolism.

Fluoroscopy is also of diagnostic value by allowing the radiologist to study the processes of lymph node filling and emptying. Spot films may be taken of both iliopelvic regions while filling is still occurring. Following introduction of the contrast material, radiographs of the pelvis, para-aortic regions, and chest are taken to visualize the lymphatic vessels and thoracic duct. Twenty-four hours later, A.P., lateral, and oblique films are taken of the pelvic and para-aortic regions by which time the ultra-fluid Lipiodol has entered the lymph nodes, rendering them radiopaque.

G. INTERPRETATION

I Assessment of the Lymphangiogram

During contrast infusion, normal lymphatics are seen as thin beaded vessels which ascend in parallel fashion along the medial aspects of both legs. The beaded areas represent lymphatic valves.[10] Near the inguinal regions, the superficial inguinal afferent vessels and node sinusoids are visualized. Three sets of channels pass through the external and common iliac nodes, giving off side-chains to the hypo-gastric groups.[7] These three chains converge and interconnect around the inferior vena cava and the aorta. Anastomosis between the right and left sides is common in the para-aortic region, but abnormal in the iliac regions. At the level of the second lumbar vertebral body, the cysterna chyli, a large calibre vessel, is formed leading to the thoracic duct which ascends in the posterior mediastinum. The thoracic duct may not be visualized if the amount of contrast material is restricted. In fact, some investigators believe that if the thoracic duct is seen, too much dye has been injected.

The upper extremity lymphatics follow the inner aspect of the arm and enter the axillary nodes. Here they branch, occasionally filling the supraclavicular nodes, and eventually draining into the subclavian vein.

What does one look for in assessing the lymphangiogram? The course and calibre of the lymph trunks and onward flow of contrast is visualized. Each node should be checked with respect to its afferent vessels, marginal sinus, sinusoidal flow pattern, hilus, and efferent vessels (see Fig. 1). Vessel displacement should be noticed as well as early sinusoidal filling of lymph nodes.[11]

Suppose lymph nodes have become obstructed: then intra-lymphatic pressure increases, causing the opening up of normally closed channels. The contrast material which has been introduced into the lymphatics will then accumulate and be forced into various alternate channels, such as perineural or perivascular lymphatics, by the increased pressure. Accessory channels are normal, functioning channels which do not opacify with the present method of lymphangiography when the system operates at usual capacity. Other such channels are the lymphovenous communications.

Therefore, important radiographic signs of lymphatic obstruction are:

(a) *Non-progression of dye*—e.g. no dye enters a para-aortic chain after having filled the common iliac nodes.

(b) *Dermal backflow and extravasation into interstitial spaces.* Lymph vessel dilatation in skin and subcutaneous tissues secondary to lymphatic obstruction will lead to lymph varices and rupture of these into the interstitium.

FIG. 1. Normal lymphangiogram. The films are taken as dye is being run in. Note the thin, beaded afferent vessels entering the node on the convex side and the efferent vessels leaving from the hilum.

(c) *Collateral vessel filling*—e.g. abdominal wall vessels, perivesical lymphatics, anastamosis with the other side below the sacral promontory, vessels seen coursing over the innominate bones.

(d) *Non-filling of normally filled channels*—e.g. if only one of three iliac channels is filled.

(e) *Displacement of channels.*

(f) *Filling of nodes not normally filled.*

(g) *Lymphovenous communications* (lympho-caval or lympho-portal). The increased intra-lymphatic pressure will cause lymph to enter the connecting channels between the lymphatic vessels and veins, the so-called lymphovenous communications. If the vein is a member of the portal system (lympho-portal), dye will collect in the liver, and if sufficient contrast material is present, the hepatic sinusoids will be opacified. If the vein is systemic (lympho-caval), dye will be found in the lungs sooner and to a greater extent than if it had taken the normal thoracic duct route.

II Assessment of the Lymphadenogram[1 2 6 11]

To best appreciate the architecture of the lymph node, the 24 hour films are looked at. In general, normal nodes vary in size with the normal maximal diameter ranging from 5 mm. to 5 cm. Most lymph nodes measure from 1-2 cm. in length. The normal nodal parenchyma is uniformly and densely stippled with contrast material. The marginal sinus is completely opacified. The node hilum will often be seen as a radiolucency. The contour of the nodes must be viewed from all angles, i.e. A.P., lateral, and oblique, in order to overcome artefacts due to superimposition of one node on another. This will also help the examiner to perceive the nodes in three dimensions.

The lymphadenogram must be compared with the lymphangiogram. In this way, a filling defect due to the hilum will be identified by the presence of efferent vessels leading from it. The fibro-fatty defects often seen in the inguinal regions will be seen to have lymphatic channels passing through, thus establishing their true identity.

Normally the internal architecture of the node has a homogeneous reticular or granular pattern. The dye is taken up by the reticular sinusoidal tissue whereas follicles do not take up much dye. Hence, an increase in lymph follicle size and/or number will lead to a decrease in density of dye in the node. The texture will seem looser.

Replacement of sinusoids by fibrosis or benign and malignant cell infiltration will also decrease the dye absorbed and give defects in the normal homogeneous contrast pattern. Thus by visualization of abnormalities of node size and pattern on radiographs, involvement by malignant and benign disease may be recognized. For instance, squamous cell carcinoma of the cervix, if present in an iliac node, will cause non-filling of part of the node (hence a "filling defect"). The fibrosis of reticular Hodgkin's disease will cause multiple smaller filling defects. Large foamy nodes are the most characteristic evidence of lymphomatous involvement. Leukemic infiltration of the sinusoid will cause a diffuse decrease in dye not unlike the picture caused by the cellular infiltrate of rheumatoid arthritis.

The inguinal nodes are often treacherous to assess because of the large number of fibro-fatty defects present. These are thought to be secondary to old leg or perineal infections. Inguinal nodes are, therefore, of little value in diagnosis unless gross abnormality is present.

Chest films should be examined carefully as contrast material reaches the lungs in all examinations.[14] In 40% of patients, it is visible on X-ray as radiopaque lung capillaries or punctiform stippling of the peripheral lung fields. If the thoracic duct is not visualized in the initial film, dye in the lungs is proof of lymphovenous communication. It should be emphasized that in the vast majority of patients no clinical manifestations accompany Ethiodol embolization.

Procedure Used in Assessing Lymphadenograms[1 2 6 11]

1. *Lymph node size:*
   (a) general impression—e.g. all nodes enlarged in diffuse lymphoma.

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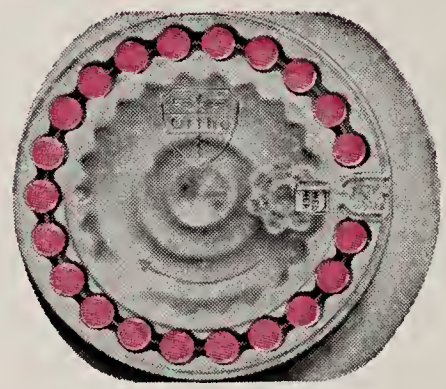

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(b) assessment of individual nodes.
(c) distribution of abnormality, e.g. focal, regional, or general.

2. *Shape:* Are the nodes round, oblong or indented? All views must be consulted to avoid superimposition artefact.

3. *Number:* Are there many small lymphoid aggregates or are there only one or two large nodes present?

4. *Pattern of contrast material:* Is the contrast distribution homogeneous or are there any filling defects? Marginal defects suggest secondary carcinoma. Central defects are indicative of lymphoma or melanoma. Is there a coarse granular pattern suggesting lymphoma or inflammatory hyperplasia?

5. *Stasis:* Is any dye still present in lymphatic channels? If so, lymphatic obstruction, perhaps secondary to carcinoma, is present.

6. *Is dye present in any place where it should not be?* e.g. (a) *Liver:* suggesting lymphoportal anastamosis.

(b) *Lymph nodes* which are not usually opacified: hilar nodes (anomalous), pre-sacral nodes (may suggest obstruction), supraclavicular nodes (anomalous—secondary deposit may be seen).

H. INDICATIONS FOR LYMPHOGRAPHY

1. Metastatic Disease

As with all other special procedures used to investigate the spread of metastatic disease, one must employ all the clinical information available. Lymphography may be used to confirm or deny a clinical impression of the spread of the disease, as well as for discovering unsuspected disease. Metastases should be expected at the sites of primary drainage as determined anatomically.[1]

Malignant emboli enter the node via the afferent channels and frequently obstruct the peripheral or marginal sinus. Thus signs of lymphatic obstruction, namely stasis of contrast material with visualization of collateral channels, will occur. The oily contrast material will outline only normally patent sinusoids, and a filling defect will result. If the entire node has been replaced *or* all the afferent channels are blocked, no dye will enter the node at all and such missing or minimally filled nodes indicate metastasis. It is well to remember that large or normal sized nodes with marginal filling defects occur in lymphadenitis or other physiological fibro-fatty defects; also confused with this will be the hila of nodes, and defects due to superimposition of two or more nodes. This can usually be avoided by carefully checking on the lymphangiogram for afferent vessels, marginal sinus, sinusoidal flow, and efferent vessels, as well as for signs of lymphatic obstruction. Multiple views of the lymphadenogram are also essential. Channels do not traverse the replaced areas but

are distorted by and circumvent the carcinomatous focus.[2] Any defect traversed by the lymphatic channels is non-malignant. Collateral circulation may be the only sign of massive nodal replacement.

Indirect signs of metastatic disease are due to lymphatic obstruction and will not be re-enumerated.

Involved glands are usually normal in size, and round (or oval in the inguinal regions) in all three projections.[6] The defect is marginal (see Fig. 2); the marginal sinus is interrupted on the lymphangiogram and a peripheral defect is seen on the lymphadenogram.[1 2] Wiljasalo's series had 87% peripheral defects, and 3% exclusively central defects.[6] The filling defect has no fixed form and may vary from a very small part to all of the node. The border is usually sharp between the normal tissue and the metastatic deposit. "Moth-eaten" is an apt descriptive term.[10] Another clue to metastasis may be the appearance of a hyperplastic reaction in glands with perishing carcinoma cells and toxic debris, i.e. if a node draining a carcinoma appears to be somewhat enlarged with a decreased density of dye, yet maintaining the normal architecture, this may be early evidence of metastatic disease.[6]

Testicular tumours act differently from most other carcinomas. Initially, nodes around the renal arteries are involved. Lymphographically, they resemble lymphomas (pseudolymphoma pattern) with the large nodes having a coarse granular or reticular pattern. Filling defects are small, multiple, and central, rather than the characteristic marginal defects usually seen in metastatic carcinoma.

Melanosarcoma (melanoma) has a characteristic appearance, having large nodes with well-defined central defects. Frequent lymph blocks are seen.[6] Thus melanoma spreads lymphatically as well as vascularly (if in fact it does spread by blood vessels at all).

At the Princess Margaret Hospital, lymphography is used to detect and delineate metastatic disease in patients with carcinoma of the cervix, corpus uteri, bladder, prostate, kidney, colo-rectum, breast, and ovary. Patients with testicular tumours and melanosarcomas are also frequently examined. The false confidence of physicians who believe that their examination of nodes either in clinic or on the operating room table is infallible has been demonstrated many times. Nodes which are thought to be malignant are benign; the reverse is also true. Lymphography merely offers another tool in the proper assessment of the patient.

Can the surgeon who does an orchidectomy for testicular tumour be certain that the para-aortic nodes are normal or abnormal, inflammatory or malignant? The size of the fields used in irradiation of nodes will obviously depend upon the number and position of nodes involved. Similarly the physician treating carcinoma of the cervix, especially in its advanced stage, can gain a great deal of new or confirmatory information.

FIG. 2. Lymphadenogram showing marginal filling defect in the node to the left of L4. This is characteristic of secondary carcinoma, in this case, carcinoma of the ovary.

Viamonte has been mixing 0.8% Chlorophyll, a green dye, with the Ethiodol. This aids the surgeon in his node dissection, as all filled nodes turn green. He is able to correlate the lymphographic with the gross findings. Unfortunately, this green dye causes stasis at 24 hours and thus removes an important sign of lymphatic obstruction. However, if lymphography with the normally used plain ultra-fluid Lipiodol is performed prior to surgery, any missed nodes will be readily apparent on radiographs taken in the operating room after lymphadenectomy. Since so many nodes are seen to remain after lymphadenectomy, it becomes evident that surgical removal is likely to be incomplete, and radiother-

apy and chemotherapy would seem, at least theoretically, to be better forms of treatment.

2. Lymphoma

In diagnosis and treatment of the lymphomas, lymphography has made its greatest contribution.[13] It is of great value in detecting the sites and extent of pathological changes involving lymphatic structures. Peters[18] describes four uses of lymphography:

(a) to determine the extent of the disease.

(b) to aid in choice of fields when irradiation is the primary approach.

(c) to act as a measure of response to a radio- or chemotherapy, because dye remains in nodes for six months, so repeat injections are *not* required.

(d) to explain obscure clinical features after treatment, such as lymphoedema in the absence of clinically demonstrable nodes.

Peters also states that "with the advent of lymphography and other specialized investigation . . . approximately 50% of these patients (with Hodgkin's disease) presenting with disease in clinical stages I and II are classified as having more advanced disease." Lower limb lymphography has, therefore, greatly increased the chances of discovering and treating more extensive disease, and thus greatly influenced the prognosis to the point where Hodgkin's disease may now be called a curable disease.[18]

Lymphomas are more readily recognized by their radiographic pattern. Love and Kim[2] state that, in general, lymphomas have one or more of the following:

(a) diffuse enlargement with a foamy or lacy pattern and a frequent increase in overall number of nodes opacified (see Fig. 3).

(b) irregular enlargement with intact margins and spotty areas of replacement.

(c) diffuse enlargement with irregular filling defects or peripheral crescentic opacities due to uninvolved subcapsular space.

The radiologic picture is due to a primary change in the intrinsic nodal architecture. The margin of the node is intact for the most part until the later stages of the disease. The lymphatics remain patent longer than in carcinoma and traverse the parenchyma and tumour tissue until they are eventually distorted and compressed. Once they are compressed, the same principles of lymphatic obstruction apply.

The following is a necessarily brief outline of the various patterns seen in lymphomatous disease.[1 2 11] But, in advanced disease, the differentiation is virtually impossible. In *lymphosarcoma,* the involved nodes are enlarged with a foamy or lacy background pattern. The

FIG. 3. Lymphadenogram showing obviously enlarged nodes with central filling defects. The foamy appearance is characteristic of lymphoma, in this case, reticulum cell sarcoma.

marginal sinus is maintained and the nodal margins are intact. *Reticulum cell sarcoma* invades the reticular portion of the node with polymorphous reticular cells and fibrillar tissue, thus losing the ability to take up dye. Early on, one gland or several glands are affected with central or marginal filling defects. The process spreads to other glands forming a coarse foamy network which may eventually block the circulation. *Chronic lymphatic leukemia* involves nearly all glands initially (difficult to distinguish from inflammation). Fine grained granulations in slightly enlarged glands are seen.[6] Later the nodes are enlarged with widespread deposits of contrast material with a reticular or circular appearance in a coarsely grained pattern. The peripheral sinuses are evenly filled with contrast material. In *Hodgkin's disease,* the glands are usually enlarged and var-

iable in deformity and filling ability. The defects seem to grow with advancing disease as the areas of replacement increase and residual rings of functioning tissue remain behind. The less aggressive forms of the disease (i.e. lymphocyte positive—nodular sclerosis, lymphocytic and histiocytic) are more typical with increased size, lacy background, and small central filling defects. More aggressive disease (i.e. lymphocyte deficient—diffuse fibrosis, reticular) has larger areas of replacement, often marginal, as well as lymphatic obstruction. Certain authors[13] have described the radiographic appearance of abnormal small nodes in the disease. Small node disease with definite filling defects is usually seen in the para-aortic regions. In view of Kinmonth's idea of the special immunological role of the para-aortic regions,[16] this type of disease may show special immunological abnormalities.

To make accurate diagnosis, radiological and pathological correlation is required. Radiologically, one samples many nodes, whereas a pathological diagnosis is often on the basis of one node. Therefore, the radiological diagnosis may in fact be more accurate and should be placed at least upon a par with the heretofore sacrosanct pathological diagnosis.

3. "Benign" Lymph Node Conditions[1 2]

Acute inflammatory disease of lymph nodes causes reactive changes in the nodes. The nodes are enlarged, but the background pattern is normal with the intensity of opacification being maintained. Acute inflammation may be local (e.g. an inguinal node draining a perineal infection) or generalized (e.g. the generalized adenopathy seen in infectious mononucleosis). A generalized systemic inflammation produces a diffuse, generalized increase in nodal size. Local inflammation, on the other hand, shows dilatation of the major lymphatic trunks draining the area with local changes in the nodes. Microabscesses may mimic filling defects of metastatic disease. Hence, the entire clinical picture is necessary.

Chronic granulomatous disease such as sarcoid may simulate lymphoma, especially Hodgkin's disease, with its diffuse lymph node enlargement. Tuberculosis may look the same but often the cavitation and necrosis present may suggest metastatic disease. The reactive hyperplasia of the collagen diseases may mimic leukemic infiltration or occasionally, with filling defects present, metastatic disease.[1]

4. Primary and Secondary Lymphedema of Limbs and Genitalia

Lymphography is an invaluable asset in differentiating between primary and secondary lymphedema as well as indicating the nature of the latter.

Lymphedema refers to edema or swelling of an anatomical region caused by lymphatic obstruction. In primary lymphedema, there is an inherent congenital structural abnormality in lymphatic vessels.[2] The condition has been described mainly in the extremities, especially the lower limb, but occurs in the upper as well. Females are more often affected (10:1). The lymphedema may be unilateral but abnormalities are always demonstrated bilaterally. The more severe the congenital defect in lymphatic channels demonstrated by lymphangiography, the earlier symptoms appear. The patient may be free of swelling for years even with marginally adequate lymphatics, but as a result of recurrent skin infections or increased intra-abdominal pressure, the lymph vessels may become obliterated and the system becomes incompetent, requiring collateral means of flow to return the lymph to the venous system. The inadequate collateral system soon fails because of poor drainage. Buonocore[4] describes four clinical syndromes —*congenital, precox, tarda,* and *senilis* reflecting the age of onset.

Lymphographically one sees signs of lymphatic obstruction. Kinmonth[3] speaks of four kinds of congenital abnormalities seen:

(a) hypoplasia — the few lymphatics present being larger than normal (most common type)

(b) dilated or varicose channels frequently associated with dermal backflow

(c) lymphatic aplasia (rare)

(d) dermal backflow without varicose channels (rare).

The abnormal flow in all cases begins in the most distal part of the extremity and is bilateral. With an increase in flow, the more proximal lymphatics are involved.

In secondary lymphedema, the lymphatic obstruction is due to anatomic obstruction by tumour infiltration, inflammation, radiation effect, surgery, or trauma. Filariasis induces lymphedema by causing fibrosis and occlusion of the lymph channels. Findings are most striking just distal to the point of obstruction. Further abnormal development appears later in the distal part of the extremity. One can often discover the etiology of lymphedema by bilateral lymphograms. In secondary disease, the contralateral limb is usually normal (unless the process is bilateral).

5. Special Problems in which Lymphography is of Aid

(a) *Chylothorax and Chylous Ascites*

This refers to the presence of chylous material in the pleural or peritoneal cavities. The cause of the condition is lymphatic obstruction anywhere between the intestinal lymphatics and the thoracic duct. As a result, chyle, the fatty material normally seen in lacteals and intestinal lymphatics draining the small bowel, is found in these cavities. The exact location depends upon the point of obstruction, but thoracic duct obstruction alone is not enough to cause this condition.[2]

Chylous reflux is either congenital or acquired. In congenital forms, a primary incompetence of lymphatic valves leads to stasis and distal lymphatic dilatation, leading to secondary distal incompetence. The acquired type is usually caused by lymphoma, carcinoma, or filariasis—any process leading to chronic lymphatic obstruction. Dilatation of lymphatics distal to the point of obstruction leads to secondary valvular incompetence. If trauma causes chylothorax or chylous ascites, the patient should be investigated for underlying pathology as a dilated thoracic duct is very prone to rupture. A lymphogram should be done in all such cases to determine the underlying pathology (e.g. lymphoma may present in this way).

(b) *Differential Diagnosis of Abdominal and Pelvic Masses*

Lymphography can be quite useful in determining the nature of an abdominal mass before a needless laparotomy is done. Most value is derived when procedures such as intravenous pyelography or inferior vena cavography are also performed. If, for example, an I.V.P. shows extrinsic deformities of the urinary bladder, a lymphogram may show these to be enlarged lymphomatous nodes. If the ureters are displaced on the I.V.P., one cannot determine if lymphoma, metastatic, or other disease is doing it. The nodal appearance on the lymphadenogram may be helpful in deciding the nature of the disease and subsequent management. Finally, enlarged para-aortic nodes may displace and/or rotate one or both kidneys laterally away from the midline. Is it lymphoma or metastatic seminoma? Lymphography with inferior vena cavography may reveal the true nature.

(c) *Chyluria*

Chyluria is the presence of chyle in the urine. When lymphatic obstruction is present above the intestinal trunk, the forces of obstruction are so great that chyle may be forced back through the lymphatic drainage of the urinary tract. Lymphatic varicosities will rupture due to the increased hydrostatic pressure giving pyelolymphatic fistulae and chyluria.[2] When this occurs, a lymphogram is in order to determine the etiology.

(d) *Protein Losing Syndromes*

Protein losing enteropathy is a well recognized condition. One of the causes of this condition is obstruction to the outflow of intestinal lymph. Hence, protein in the chyle is lost via the G.I. tract. By a similar mechanism, protein losing uropathy secondary to lymphatic obstruction is occasionally seen. When the etiology of these two conditions is not readily apparent, a lymphogram may reveal lymph node or vessel disease.

6. Therapeutic Applications
(see Recent Advances in this issue)

I. COMPLICATIONS

Dolan, in 522 cases reported fever in 97, nausea and vomiting in 23, local foot pain in 17, respiratory symptoms in 7, and a rash in 5.[12] Other complications include local sepsis, extravasation of dye, pain during injection, delayed wound healing, skin and urine discoloration (blue dye). Davidson reported that 15-20% of patients had mild febrile reactions in the first 48 hours, or else local pain.[11] To overcome this, he routinely advises bed rest for 48 hours.

The most severe complications are the respiratory and allergic ones. The respiratory problem is easy to explain: all the water insoluble dye leaving the thoracic duct will go into the lungs via the pulmonary arterial circulation, thus producing Ethiodol pulmonary embolism. Gold showed a transient decrease in pulmonary function after lymphography even when dyspnea was absent.[19] In Bron's series, 55% showed radiographic evidence (fine stippling in the lung fields).[20] But this may have been due to the use of too much contrast medium or poor monitoring during the filling phase, thus missing the lymphovenous communication. Correcting these two factors and also avoiding patients with poor respiratory function will decrease the respiratory complications. The other serious complication is Ethiodol hypersensitivity reaction and can usually be avoided by taking a careful allergic history. A history of iodine sensitivity is a contraindication.[11 12]

CONCLUSION

Lymphography, therefore, can be an invaluable investigative procedure in a wide range of clinical problems. People have objected to it as being too time-consuming a procedure. However, if one is equipped to do it on a regular basis, the time and personnel required can be kept to a minimum.

With respect to the lymphomas, no one would deny the effect of lymphography on diagnosis, advancement of clinical staging, and evaluating treatment. Davidson and Peters report a 36% gain in accuracy of clinical staging, and that in 62.5% of 40 patients, retroperitoneal disease was discovered.[13] Love and Kim also emphasize its use and accuracy in lymphedema.[2]

The value of lymphography in detection of metastatic disease is controversial. Schaffer states that lymphography is of less value in patients with carcinoma than those with lymphoma, for some lesions are too small to be detected as filling defects; completely replaced nodes will not be visualized; and there may not be signs of obstruction and backflow or of collateral circulation.[14] Non-malignant filling defects may be difficult to distinguish, and some pelvic nodes are not visualized. Hence, he emphasizes that a negative investigation does not rule out the possibility of metastatic disease and that the total extent of lymph node metastases therefore

should not be determined from the lymphogram alone. O'Leary and Friedman also point out with respect to pelvic carcinoma that lymphography is not useful in the early diagnosis of carcinoma of the cervix.[15] It is more valuable in advanced disease to determine extent and to follow the treatment. However, they do state, as does Herman,[7] that the major lymph nodes of the cervix, the so-called obturator nodes, are external iliac nodes and as such are always opacified.

Kinmonth[16] reports good results using lymphography in the diagnosis and treatment of melanosarcoma. Davidson reports that "encouraging results have also been obtained in detecting metastatic carcinoma" and with future refinements in technique may prove to be of great benefit. "Micrometastases in lymph nodes can be excluded only by operation and histological examination; however, in patients with cancer, lymphography can demonstrate metastatic involvement of lymph nodes before there is clinical evidence."[11]

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Multiple Myeloma

G. R. French 6T8

Immunoglobulins normally are produced by the cells of the reticuloendothelial system only as a response to antigenic stimulation. Multiple myeloma is considered to be due to a neoplastic proliferation of probably one (or, based on the evidence of a few reported cases, perhaps two) clone of these immunologically competent cells.

Large quantities of these proteins, which are physiochemically and immunologically related to normal gamma globulins, are produced. These proteins probably are devoid of any antibody function (at least, up to the present time, no one has ever found an antigen to which these proteins are the complimentary antibody).

ETIOLOGY

The etiology of this disease remains as unknown as it was when it was first described by John Dalrymple, Henry Bence Jones and William MacIntyre in 1846 and 1850, all of whom had been called in consultation to see Mr. T. A. McBean, a 45 year old Scottish grocer, who is recorded as being the first patient ever to have medically diagnosed multiple myeloma. This patient demonstrated many of the classical features of the disease including bone pain, fractures and Bence Jones protein (which really was first discovered and described by Dr. MacIntyre).

DIAGNOSIS

A. Clinical Findings

(a) *Symptoms*

Feature and Mechanism

1. Bone pain — Fractures, compression.
2. Weakness and Fatigue — Anemia, azotemia.
3. Polyuria, Polydipsia — Azotemia, increased Ca^{++}.
4. Bleeding tendency — Thrombocytopenia, interference with function of clotting factors.
5. Infections—Dysgammaglobulinemia, leukopenia.
6. Joint pain — Bone destruction, amyloid deposits.

(b) *Signs*

1. Signs of congestive failure — Anemia, amyloid infiltration of the heart.
2. Palpable tumors — Plasmacytoma.
3. Weight loss, cachexia — General characteristics of malignancy.
4. Pallor — Anemia.

B. Radiological Findings

1. Widespread, discrete, punched out lesions throughout the skeleton.
2. Diffuse marrow infiltration giving X-ray appearance of osteoporosis.
3. "Soap bubble" tumors.

C. Hematological Findings

(a) *Periphereal blood*

1. Anemia — normocytic normochromic, or macrocytic hyperchromic (due to decreased folic acid).
2. Elevated ESR.
3. Background stain to film.
4. Rouleaux formation.
5. Occasional plasma cells in buffy coat or peripheral film.

(b) *Marrow*

1. Infiltrated with plasma cells and reduction of other marrow elements.

(c) *Sia's Test*

1. May be positive
(screening test for macroglobulins)

D. Biochemical Findings

1. Hypercalcemia (bone resorption).
2. Hyperuricemia (cause unknown).
3. Elevated B.U.N., decreased creatinine clearance (myeloma kidney).
4. Alkaline phosphatase normal (usually).
5. Elevated total plasma protein, reversed A/G ratio.
6. Homogeneous globulin peak — paper electrophoresis.
7. IgG or IgA elevated — immunoelectrophoresis.
8. Normal immunoglobulins decreased — immunoelectrophoresis.

E. Urinary Findings

1. Bence-Jones proteinuria (about 50% of cases).
2. Casts — usually hyaline unless infection present.
3. Infection (often).

The usual age range for the disease is 30 to 80 years. In some series, males have outnumbered females by two to one; others report a nearly equal sex incidence.

The patient with multiple myeloma most commonly presents with a combination of bone pain, weight loss and anemia. On occasion, the diagnosis is made as a result of investigation for unexplained anemia, leukopenia or bleeding tendency. Sometimes the patient complains only of excessive fatigue. Other initial features may be repeated infections, circulatory disturbances or neurological complaints. One should always keep in mind the idea that myeloma may present as a real diagnostic problem, the correct diagnosis requiring considerable perspicasity on the part of the physician.

DISCUSSION OF CLINICAL FINDINGS IN MULTIPLE MYELOMA

1. *Pain:*

In a series of 72 patients, all with proven myeloma, described by Whitelaw[14], the presenting symptoms were as follows: pain — 59, fatigue and weakness — 6, disease discovered by accident — 2, lump noted after trauma — 1, pneumonia — 1, weight loss — 1, bleeding — 1, paraplegia — 1. The sites of initial pain in this series were: chest, ribs and dorsal spine — 24; low back — 21; pelvis or femur — 6; neck, forearm or sternum — each 2.

The patients were surveyed as to the causation of pain and the following were the findings: abrupt onset of pain meant a fracture at the site of the pain. One half of those with gradual onset of pain had a fracture at the painful site. The majority of osteolytic lesions were painless.

2. *Bone:*

Myeloma is characterized by the development of multiple tumours of bone marrow which produce pain, pathological fractures and anemia.

The most common X-ray appearance is that of multiple punched out bone lesions of varying sizes, with well defined margins. These lesions are seen most commonly in bone overlying the sites of active marrow in the adult (i.e. skull, ribs, vertebrae and pelvis). There is little osteoblastic activity and the alkaline phosphatase is usually normal. Extensive destruction of bone causes marked calcium resorption with consequent hypercalcemia (and the complications of the latter).

Other bony lesions are also seen, such as diffuse osteoporosis (in 25% of cases), or solitary myeloma (plasmacytoma). The solitary myeloma, which tends to progress to generalized disease, presents as a multiloculated bony expansion, and because of its X-ray appearance has been termed a "soap bubble tumor".

In the course of the disease, a patient may demonstrate one or all of these X-ray findings.

Fractures of the vertebral column may lead to shortening of stature, pressure on nerve roots or even cord compression. Fractures of the ribs can lead to pleuritic pain, shallow breathing and poor cough.

3. *Joints:*

Occasionally arthralgia is a problem, and may result from bone destruction or amyloid deposits in the joints.

4. *Peripheral Blood:*

Common findings are anemia, elevated ESR (often to markedly high levels in the range of 100 - 150 mm/hr), leukopenia and a low platelet count.

The blood film often has a bluish-gray background stain due to the increased level of circulating gamma globulin; marked rouleaux formation and on occasion plasma cells are seen. A film made from the "buffy coat" concentrate may be used to assist in determining if plasma cells are present in the peripheral blood.

Anemia may be due to replacement of the erythropoietic tissue in the marrow by plasma cells, chronic

TABLE I — NOMENCLATURE AND SOME PHYSIOCHEMICAL PROPERTIES OF HUMAN IMMUNOGLOBULINS (AFTER SCHWARTZ)

	IgG	IgA	IgM	IgD	B-J Protein
Sedimentation Coefficient	7s	7 (9, 11, 13) s	19s	7s	2.4 — 3.5s
Molecular Weight	160,000	160,000	900,000	—	22 — 44,000
Carbohydrate Content	2.5%	10%	10%	—	0%
Electrophoretic Mobility	Slow γ_2 Fast γ_1	Fast γ_1	Fast γ_1	Fast γ_1	—
Heavy Chain Mol. Wt. = 50,000	γ	α	μ	δ	—
Light Chain Mol. Wt. = 20,000	K (60%) or λ (40%)	K or λ	K or λ	K or λ	K or λ
Molecular Structure	γ_2K_2 or $\gamma_2\lambda_2$	α_2K_2 or $\alpha_2\lambda_2$	μ_2K_2 or $\mu_2\lambda_2$	δ_2K_2 or $\delta_2\lambda_2$	K or λ*

**Bence Jones Protein may consist of either K or light chains depending upon whether K or light chains are found in the myeloma portein molecule. (Schwartz)*

renal disease (myeloma kidney) which causes cessation of erythropoietic activity (uremia), GI bleeding, or drug toxicity.

5. *Bone Marrow:*

The appearance of the marrow is highly variable depending upon the extent of the disease; however, this examination is the single most important diagnostic test as myeloma may be diagnosed by the appearance of the marrow alone. Usually there is an increase in the total number of plasma cells, in which there is an increase in the nuclear/cytoplasmic ratio.

The progressive proliferation of plasma cells eventually forces the other elements of the marrow into oblivion, with the consequent development of anemia, leukopenia, and thrombocytopenia.

Very rarely, a plasma cell leukemia will develop.

6. *Cardio-Vascular System:*

See Diagnosis previously.

7. *Kidney:*

About one-half of patients with this disease develop Bence-Jones proteinuria *(vide infra).*

The kidneys are frequently affected; one series of cases showed autopsy evidence of renal disease in 86% of cases. Kidney damage results from tubular obstruction and dilatation associated with deposits of Bence-Jones protein within the lumen of the tubules. This may extend from the distal tubules to high in the proximal convoluted tubules. In some cases, an adult Fanconi syndrome has occured because of the impaired ability of these damaged tubular cells to reabsorb glucose, amino acids and salts. Eventually, renal failure with azotemia occurs.

Other mechanisms cause renal damage as well: (i) a high frequency of pyelonephritis, (ii) hypercalcemia may cause nephrocalcinosis, (iii) amyloid may be deposited in the renal blood vessels and glomerular tufts, and (iv) uric acid crystal precipitation in the tubules and/or the formation of uric acid stones with consequent obstruction of the urinary tract.

8. *Nervous System:*

Numerous mechanisms are involved here: (i) vertebral collapse causing nerve root compression with radicular symptoms, (ii) expanding plasmacytomas may cause stretching of cranial nerves, compression of the cord or pressure on peripheral nerves, (iii) amyloid may infiltrate peripheral nerves causing weakness and paresthesias, (iv) a polyneuropathy unrelated to amyloidosis has been described. This is a degenerative condition of the peripheral nerves which may either affect the lower limbs alone or the upper limbs as well, with consequent sensory and motor symptoms of the lower neuron type.

LABORATORY FINDINGS

Sixty percent of patients with myeloma have an increase in their serum globulin, and characteristically their A/G ratio is reversed.

On paper electrophoresis the abnormal globulin usually migrates with the gamma globulin or between the gamma and the beta regions, the "M" fraction, or less frequently in the beta or alpha regions[1]. The appearance of the myeloma protein on the electrophoretic strip is that

of a narrow spike forming what is referred to as a homogeneous peak. The abnormal immunoglobulins may be assigned to either the gamma-G (65%), gamma-A (30%), or rarely the gamma-D class on the basis of the physiochemical and antigenic properties of their heavy chains which are designated as gamma, alpha or delta respectively[9].

Unlike normal gamma globulins which consist of a mixture of molecules having either the Kappa (60%) or Lambda (30%) variety of L (light) chains, "M" component molecules uniformly possess either one or the other antigenic type of light chain only[9].

The presence of two major "M" components in the serum of patients with multiple myeloma is rare but has been reported.

The type of abnormal immunoglobulin produced varies from patient to patient but remains constant in any given patient throughout the course of his disease. The quantity of protein produced varies within the course of his disease.

Bence Jones protein (see Table I) appears in about ½ of cases with myeloma but also has been found in small quantities in the serum and urine of normal individuals. This protein which is identical with the L (light) chains of immunoglobulin molecules has a unique property when subjected to heat. When urine which contains B-J protein is heated to 45-50°C, the protein (including B-J protein) precipitates. When the boiling point is reached, the B-J protein redissolves and then reappears when the urine is cooled. B-J protein is detectable by the heat, nitric acid or sulfacylic acid tests for proteinuria but not by the stick tests (*e.g.* Labstix or Albustix).

There is an inverse relationship between the occurrence of Bence Jones proteinuria and the level of serum gamma globulins (the same relationship is true for the development of amyloidosis).

"Myeloma cells" may not be detectable in the marrow of patients with solitary plasmacytomas, and indeed, abnormal protein may not be found in their serum.

COMPLICATIONS

1. *Infectious* complications are the most common cause of death in patients with this disease. Recurrent pneumonias, septicemias and urinary tract infections are all very frequent occurrences.

There are a number of predisposing causes to infection: (i) the treatment of the underlying malignancy with cytotoxic agents causes bone marrow depression with consequent leukopenia or aggrevation of pre-existing neutropenia; (ii) it is theorized that the high level of abnormal antibody production "turns off" production of functional antibody by the normal cells of the reticuloendothelial system by means of a feedback system; (iii) the frequent occurance of pathological fractures (and consequent severe pain) leads to immobilization in bed and shallow breathing which predispose to pneumonia.

2. *Amyloidosis:* Amyloid disease has been reported as occuring in from 6-15% of patients with myeloma.[16] Amyloid occurs frequently in, but is not restricted to, patients with Bence Jones Proteinuria.

Amyloid is a fibrous protein with a characteristic ultrastructure quite distinct from that of gamma globulin. It is an amorphous, eosinophilic, glassy, hyaline extracellular substance which may infiltrate all body systems, and is characterized by metachromatic staining.

Organomegaly (especially of the liver, spleen, kidneys and heart) may be marked when amyloid deposits in these organs are large. The G.I. tract may be involved and ulceration of the stomach and intestines is not uncommon. The disturbance of vital functions associated with amyloid deposits depends upon the physical presence of amyloid and not upon an inflammatory response. Symptomatology does not appear until amyloid has virtually replaced the entire substance of the organ.

An excellent account of specific organ involvement and clinical manifestations caused by amyloidosis will be found in a recent article by A. S. Cohen[14].

DIFFERENTIAL DIAGNOSIS

Myeloma must be differentiated from rheumatoid arthritis, for, in the latter disease the patient may show diffuse hypergammaglobulinemia, plasmacytosis of the bone marrow and amyloidosis. However, with R. A. the latex fixation test is often positive and joint involvement and subcutaneous nodules are characteristic. Myeloma must be differentiated from the macroglobulinemia of Waldenstrom (in which the globulin elevation is in the IgM region) and Heavy Chain Disease of Franklin (in which there is a rapid onset of painful, tender adenopathy, fever and splenomegaly).

Differentiation from other leukemias and lymphomas is on the basis of lymph node and marrow biopsies.

The protein abnormalities appearing in electrophoresis differentiate the hypercalcemia of myeloma from that occuring with primary hyperparathyroidism and the myeloma kidney from other causes of azotemia.

If the homogeneous, (narrow) peak of protein occuring in myeloma is kept in mind, differentiation will be easily made from the diffuse hypergammaglobulinemia and bone marrow plasmacytosis occuring in various inflammatory and infectious diseases.

TREATMENT OF MULTIPLE MYELOMA

As with any illness, treatment comprises both supportive care and specific measures. The importance of ambulation should be emphasized since skeletal decalcification

is hastened by immobilization. Hydration is important whenever hypercalcemia or hyperuricemia are present.

Complications of the disease, eg. congestive heart failure and azotemia, should be treated by standard methods. Anemia may be remedied by blood transfusion, folic acid and steroids.

Local irradiation to a painful site will produce relief within a few days, "far more quickly than could have been accounted for by healing and stabilization of a fracture." Therefore, perhaps radiation acts on extruded tumour tissue.[14]

In the past, ethylcarbamate (Urethane) was the drug of choice in the treatment of this disease, but this has now been supplanted by the alkylating agents which act on DNA. This latter group (which are termed "radiomimetic" because their effect is similar to that of radiation therapy) consists of cyclophosphamide (Procytox), chlorambucil (Leukeran) and phenylalanine mustard (Melphelan, Alkeron).

Melphelan is the drug of choice for the disease. Its use frequently gives dramatic subjective and objective benefits and remissions which may last for months. Therapy has to be stopped if drug induced agranulocytosis occurs. Sooner or later the patient becomes refractory to Melphelan and one should then change to another cytotoxic agent.

Cyclophosphamide has been shown to be about equally as effective as Melphelan in the therapy of this disease.[3]

The use of adrenal steroids may be justified in patients with hemolytic anemia or hypercalcemia but one should always bear in mind the side-effects of these drugs, especially osteoporosis and predisposition to infection.

Infectious complications are treated with antibiotics to which the organism is sensitive, and perhaps gamma globulin.

PROGNOSIS

The prognosis for patients with myeloma is uniformly bad, most succumbing to the disease within two or three years of the malady becoming symptomatic. However, the course of the illness is quite variable and some patients may live for many years.

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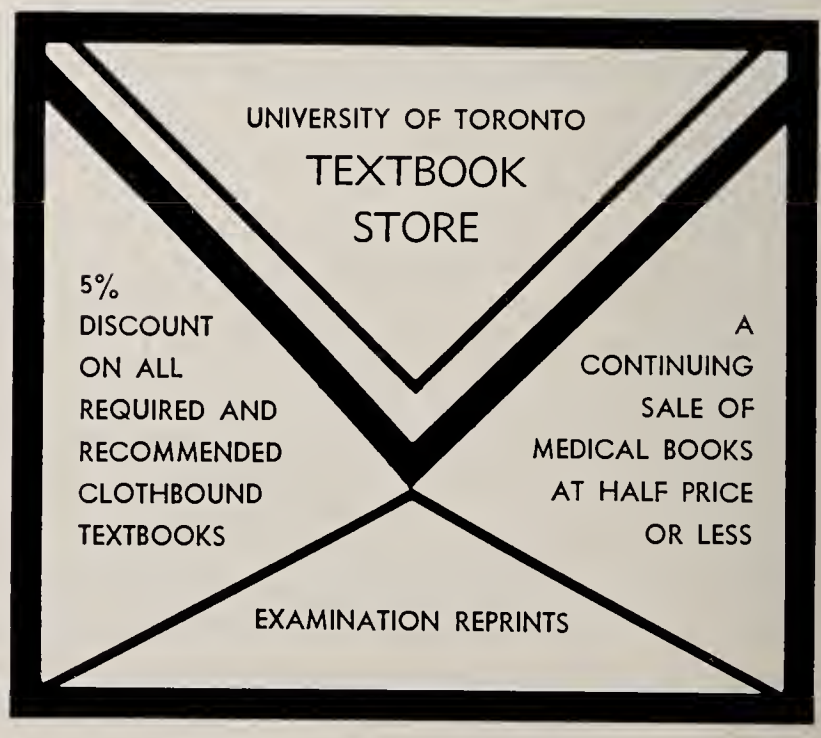

Fundamentals Of Radiologic Examination

Special Techniques

In this final issue of Volume XLV, several special radiologic techniques not dealt with in previous issues will be presented. These procedures, mainly utilizing contrast media, are for the most part not in widespread *routine* use—rather they are largely the domain of the specialist and subspecialist. Because of this, and because of the large number of such techniques, a detailed description of each will not be given—just a brief account of the procedure, the indications for its use, and the information which may be derived. For the same reasons there will be no sample radiographs in this issue.

I URINARY TRACT RADIOLOGY

Intravenous and retrograde pyelography were discussed by Mr. Cohen in the last issue. A discussion of those techniques "from the bladder down" (with the exception of renal arteriography and retroperitoneal pneumography) will follow.

1. Cystography

This method, whether it be by the intravenous route or by direct catheterization of the bladder, is usually combined with the respective type of pyelography—intravenous or retrograde. However, at times just cystograms or cystograms combined with other examinations of the lower urinary tract (e.g. cystourethrograms) are indicated. These techniques are all retrograde in type, involving catheterization. Indications include the following:

a) when a cystoscope cannot be passed to the bladder, but a catheter can, e.g. small urethra in male children, occlusion of the urethra in adult males, as with stricture and prostatism.

b) when rupture of the bladder is suspected e.g. pelvic trauma.

c) when other abnormalities of the bladder are suspected e.g. diverticula, filling defects (calculus, tumour).

d) when ureterovesical reflux is suspected, e.g. neurogenic bladder, obstruction of the outflow tract at, or distal to, the bladder neck.

Symptoms which lead to this type of examination in selected cases are: hematuria, the triad indicating infection of urgency, frequency, dysuria (especially if recurrent), incontinence—stress or urgency, and persistent bacilluria—symptomatic or asymptomatic.

2. Cystourethrography

The demonstration of functional defects of the bladder, especially ureterovesical reflux is often inadequate by simple cystography as described above. Delayed films taken every 15-30 minutes for 1-3 hours have been found to reveal this reflux more efficiently. An even better method, however, involves taking films by cineradiographic techniques (using fluoroscopic control with an image intensifier) during the act of voiding. At this time intravesical pressure is highest and reflux up the ureters is seen as the bladder contracts. This type of cystography is usually combined with urethrography and is called *voiding cinecystourethrography*. Indications for its use are:

a) when anatomic defects of the bladder and urethra are suspected. Some examples were discussed above; others include bladder neck obstruction, posterior urethral valves, cystocoele and urethrocoele.

b) when functional defects of the bladder and urethra are suspected. As mentioned these are seen best during voiding. The best example of course, is ureterovesical reflux. In the investigation of children especially, in whom congenital obstructive deformities predispose to elevated intravesical pressure, reflux, stasis and recurrent infection leading to renal failure, the radiologist plays a key role. In cases found early enough, surgical repair of the ureterovesical junction (in addition to correction of any primary cause of the reflux) can save the life of the patient. Symptoms or signs in children which should alert one to the presence of urinary tract abnormalities include enuresis—nocturnal or diurnal, recurrent infection (frequency, urgency, dysuria, pyuria), hematuria, abnormalities in the urine stream, and most important, any unaccountable disturbance in growth and development.

3. Urethrography

This procedure is rarely done alone but may be useful in cases of obstruction distal to the bladder neck as in stricture and prostatic enlargement.

4. Renal Arteriography

Contrast material is injected by either of two methods: the first is *translumbar aortography* in which a percutaneous needle is placed in the aorta. The renal vessels are outlined but the method is not as efficacious as *retrograde femoral catheterization* in which selective catheterization and visualization of the renal arteries is possible. The former method is still used in cases in which tortuosity and atherosclerosis of the iliac vessels does not allow one to insert a catheter in a retrograde fashion.

Renal arteriography is useful in three main instances: the differentiation of renal tumours and cysts; the investigation of hypertension; and the identification of

aberrant arteries which may block the ureter. Renal tumours (hypernephromas) characteristically are very vascular, whereas the typical cyst appears as a rounded defect on the arteriogram. A significant number of hypertensive patients suffer from secondary hypertension due to renal ischemia. This may be caused by atheromatous deposits in the renal arteries, or stenosis from other causes (embolus, thrombus, fibromuscular hyperplasia etc.). Many of these lesions can be detected by renal arteriography.

5. Retroperitoneal Pneumography

In this procedure air, oxygen, or carbon dioxide is introduced into the retroperitoneal space. The older method of direct injection into the perirenal space has been abandoned because of the danger of air embolism. Presently, the technique involves insufflation via a needle inserted into the retroperitoneal space between the tip of the coccyx and the rectum. This is known as *presacral pneumography*. To allow the gas to reach the perirenal area the head of the patient's bed is elevated about 20°. Plain films are taken every 30-60 minutes until maximum delineation of the kidney and adrenal is obtained. At this point tomograms are done. Complications include air embolism (extremely rare) and "surgical" emphysema of the mediastinum and neck. To prevent these the examiner should always aspirate the needle prior to injection and the patient should lie flat for 6 hours following insufflation. In addition carbon dioxide, with its greater solubility in body tissues and blood, has been recommended as an added safety feature. Besides this it is absorbed more rapidly, requiring shorter immobilization of the patient.

The major use of this procedure is in the investigation of retroperitoneal masses, irregularities of renal outline (as in hypernephroma), and adrenal tumours and hyperplasia. Because of its potential dangers it should not be employed until other conventional methods of investigation have been attempted unsuccessfully.

II NEURORADIOLOGY

1. Pneumoencephalography and Ventriculography

In ventriculography the ventricles are filled with air by direct puncture of the brain through a posterior parietal burr hole. In recent years, however, pneumoencephalography—the injection of air into the spinal subarachnoid space with the patient in the upright position—has largely replaced the former technique. In addition to visualization of the size and position of the ventricles, pneumoencephalography offers the advantage that the subarachnoid space (spinal, cerebral, and basal cisterns) may be outlined. Ventriculography is still sometimes used when there is clinically increased intracranial pressure (particularly in obstructive internal hydrocephalus) with the attendant danger of herniation of the cerebellar tonsils through the foramen magnum.

These air studies are useful in the diagnosis and localization of hydrocephalus, space-occupying lesions (particularly infratentorial; supratentorial lesions are more easily seen by carotid arteriography), and cerebral atrophy.

2. Myelography

This technique, analogous to pneumoencephalography, involves the intrathecal injection of an iodinated oil contrast medium into the spinal subarachnoid space. By tilting the patient under fluoroscopic control, the entire space may be visualized. After the procedure the oil is removed. Ruptured lumbar and cervical discs, and subarachnoid block due to spinal cord tumours, etc., may be demonstrated in this way. Myelograms are not indicated for all patients with root signs neurologically, but only when surgery is contemplated (for confirmatory pre-operative localization) or a spinal cord tumour is suspected.

Sometimes, especially in posterior fossa tumours where air studies are not sufficient, oil contrast media is injected directly into the ventricles, analogous to ventriculography and is called *positive contrast ventriculography*.

3. Discography

This procedure which involves direct injection of a water soluble dye into the nucleus pulposus of an intervertebral disc has not yet gained widespread use. The essence of the test is to reproduce the same pain the patient experiences clinically when contrast media is injected into the degenerated disc. This may be helpful if the myelogram fails to demonstrate a herniated disc, but because it depends on subjective evidence, the reliability of the test is still open to question. The radiologic appearance of the nucleus may also serve as a guide to degeneration. Based on this, one possible use of the technique is in pre-operative assessment of intervertebral discs above and below the proposed site of fusion. The presence of degeneration in the adjacent discs may lead the surgeon to extend the fusion and avoid additional surgery in the future.

4. Cerebral Arteriography

Contrast material in the *carotid* artery outlines the supratentorial vasculature (anterior and middle cerebral arteries) on the side of the injection. In the *vertebral* artery there is opacification of the basilar artery and the infratentorial vasculature (posterior cerebral and the cerebellar arteries) bilaterally.

The methods include direct injection of the carotid or vertebral vessels in the neck or retrograde injection (by a special pressure pump apparatus) of the brachial artery. This latter technique outlines both the carotid *and* vertebral systems on the right and therefore is usually used on that side. However, on the left side only the vertebral system is demonstrated. The reason for this is the different anatomy of the vasculature in-

volved i.e. the origin of the common carotid artery (the student may review this in any anatomy text). Consequently when the carotid system is to be visualized on the left side, injection of the artery in the neck is necessary.

Vascular lesions diagnosed commonly by arteriographic techniques include: (1) aneurysms (2) arteriovenous malformations and angiomas (3) arterial occlusion by thrombosis, embolism, or atherosclerosis and (4) hemorrhage and hematoma formation (subdural and intracerebral). Arteriography is also useful in demonstrating space-occupying lesions such as abscesses and tumours—either by shift of the normal vascular pattern or by a localized increase in vascularity. This latter sign is particularly useful in the diagnosis of meningioma—a potentially curable surgical lesion.

III VASCULAR RADIOLOGY

1. Arteriography

The lower limb is examined by needle puncture of the femoral artery in the groin; the upper limb via the axillary or subclavian arteries; the head and neck via the common carotid, vertebral or brachial arteries (see above), and the aorta via translumbar percutaneous puncture or retrograde femoral catheterization. The thoracic aorta can also be examined by transaxillary catheterization. The major clinical uses of arteriography are in the investigation of vascular disease, and the diagnosis and differential diagnosis of tumours and cysts.

a) *Vascular Lesions*

The vascular lesions that may be diagnosed by arteriography include 1) atheromatous stenosis and thrombosis 2) embolism 3) aneurysms 4) arteriovenous fistulae and 5) angiomatous malformations.

b) *Tumours and Cysts*

Maligant tumours are often more vascular than normal tissue, benign tumours, or cysts. Arteriography makes use of this fact and often enables deep-seated tumours to be localized. In many cases not only can the tumour be localized but the pattern of vessels may be a clue to its pathological type.

2. Phlebography

This procedure is mainly used in the investigation of venous problems in the lower extremities—especially deep venous thrombosis and its complications. Venograms can demonstrate whether the deep system is patent and whether the valves (deep and communicating) are competent.

Two other special examples of this technique bear mention. *Inferior vena cavography* has been used to demonstrate internal occlusion by embolus (usually), thrombosis, or tumour. Also it may be externally occluded by enlarged retroperitoneal lymph nodes in lymphoma and metastatic carcinoma.

Splenoportal venography is a relatively new procedure with widespread applications. A needle is introduced into the spleen and the splenic pulp pressure (which reflects portal vein pressure) taken. Dye is then injected which gradually fills the splenic vein, portal vein and any collateral channels that may be present, e.g. esophageal veins when portal pressure is increased. The detection of esophageal varices is the most common clinical application of this technique and for doing so, it is more reliable than a barium swallow. Other indications include the investigation of unexplained splenomegaly, portal hypertension, peculiar upper G.I. bleeding, pre-operative assessment in patients considered for portacaval shunts, and to demonstrate the patency of spontaneous or surgical portacaval anastamoses.

3. Lymphography

This technique is considered in detail elsewhere in this issue by A. S. Gordon.

IV BILIARY TRACT RADIOLOGY

1. Oral Cholecystography

In this procedure the patient takes the contrast medium by mouth. After absorption by the gut the liver excretes the dye in the bile and it is concentrated by the gall bladder. Films are taken 16 hours after the ingestion of the medium and, provided absorption and liver function are adequate, should show a *normal*, functioning gall bladder filled with dye. The patient is then given a fatty meal (intravenous cholecystokinin is rarely used) to induce gall bladder contraction. Additional films should then show it to have contracted well and may (but certainly will not always) demonstrate the cystic and common bile ducts. Oral cholecystography is not the procedure of choice when the duct system is to be visualized.

Calculi in the gall bladder will be demonstrated as filling defects provided that the gall bladder is functioning (to concentrate the dye) and provided that the cystic duct or Hartman's pouch is not obstructed. Failure to opacify is highly suggestive of non-function or obstruction, but is not conclusive since the presence of dye also depends on intestinal absorption and hepatic excretion.

Oral cholecystography is the routine method of investigating persons with suspected gall bladder disease. If the gall bladder fails to opacify on one examination it is usually repeated once or occasionally twice. If these examinations are done in close temporal sequence (like on successive days) the efficacy of the procedure may be improved. This is because some of the original

dose is reabsorbed and re-excreted by the liver. Indications for cholecystectomy on the basis of this test (provided that clinically there is a good history of biliary colic and/or acute cholecystitis) include demonstration of calculi or failure of the gall bladder to opacify on two examinations.

2. Intravenous Cholangiography

In this procedure, because a bolus of dye is injected intravenously, a higher concentration reaches the liver at once, resulting in a reliable demonstration of the extrahepatic biliary ducts (and sometimes the larger intrahepatic radicles if they are dilated due to obstruction). The gall bladder may show up as well if it is not obstructed, but this technique is not as reliable as the oral method for demonstrating gall bladder calculi.

Timing of the films following injection depends on the results noted on the first film but the usual spacing is 20, 30, 45 and 60 minutes. An intravenous cholangiogram (I.V.C.) is indicated in the following circumstances:

1. Following cholecystectomy in patients with recurrence of symptoms suggesting biliary tract obstruction.
2. Whenever disease of the common bile duct is suspected, as in patients with intermittent obstructive jaundice. Usually the I.V.C. does not show anything if the serum bilirubin is greater than 1 mg. % but it may show results up to 4 mg. %. For this reason the examination may be helpful in cases of intermittent or partial obstruction such as occurs with common duct stones, spasm of the sphincter of Oddi or stricture formation. However it usualy is *not* helpful in unremittent progressive obstruction as seen in carcinoma (pancreas, ampulla, ductal etc.), since the liver cannot excrete the dye. The cause of the obstruction, e.g. calculus, may itself be seen but more often the effects are obvious, such as dilatation and tortuosity of the common duct, hepatic ducts, and even the larger intrahepatic radicles as mentioned previously.
3. An emergency I.V.C. may be helpful in the differential diagnosis of acute cholecystitis. If the extrahepatic duct system is visualized, but not the gall bladder, it is suggestive of cystic duct obstruction and therefore, acute cholecystitis.

3. Percutaneous Transhepatic Cholangiography

This procedure is indicated only in patients with obstructive jaundice in whom the level of obstruction is obscure, in whom the decision to operate or not must be made promptly, or in whom laparotomy is not preferred.

A needle is introduced through the surface of the liver by percutaneous puncture. There is usually little difficulty in entering the lumen of an intrahepatic duct if dilatation is present. This is ascertained by the aspiration of bile, following which the dye is injected. In intrahepatic obstruction the larger ducts are normal in size, or may not be demonstrable if the obstruction is severe. In extrahepatic obstruction, depending upon the location, the hepatic and/or common duct may be enlarged and tortuous proximal to the obstruction.

4. Postoperative T-Tube Cholangiography

In biliary surgery, there are certain indications (which will not be reviewed here) for leaving a T-tube in the common duct in order to secure adequate biliary drainage. Contrast material can later be injected directly into the tube under fluoroscopic control, and the ductal system visualized well. This should be done in all cases of T-tube drainage before removal of the tube to ensure that the ducts are patent and draining well.

5. Operative Cholangiography

A small tube is inserted into the cystic duct at operation and the bile ducts filled with contrast medium. Films are taken and examined immediately so that any residual calculi in the ducts can be removed. This is routine in cholecystectomies at some centres.

V GYNECOLOGICAL RADIOLOGY

Hysterosalpingography

In this technique a radio-opaque oil is introduced by cannula into the uterus via the cervix. The injection is continued until the Fallopian tubes are filled and some dye spills into the peritioneal cavity. Films are taken at various intervals during the procedure. One can thus estimate the size and shape of the urterine cavity and the size, shape, and patency of the Fallopian tubes. The main use is in the investigation of infertility (tubal patency and uterine anomalies); other indications for its use, such as the detection of intrauterine pathology causing excessive bleeding, are less concrete. The examination is more reliable than the older method of air insufflation in which air was similarly introduced and radiologic evidence of air in the peritoneal cavity (under the diaphragm) was sought. In this latter method the incidence of false postives and negatives was high. In hysterosalpingography, false positives do occur (although to a lesser degree). Bilateral proximal (to the uterus) tubal obstruction due to spasm occasionally is a problem as well. Contraindications include active infection of the genital tract, recent or active uterine bleeding, suspected pregnancy, genital T.B., and severe systemic disease involving the cardiorespiratory system.

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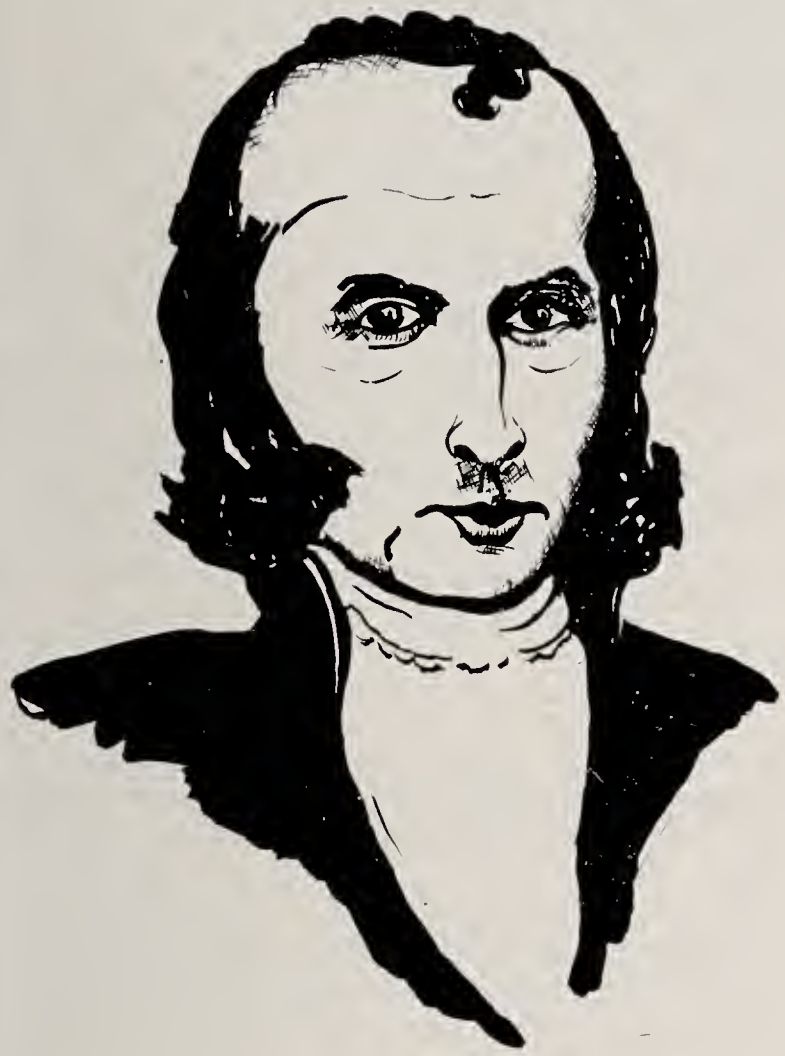
Thomas Hodgkin (1798-1866)



"Doubtless, if the governors of Guy's Hospital had appointed Hodgkin to their staff, medicine would have been enriched still further, for no young physician ever gave greater promise."

This quotation aptly describes the unrealized potential of Thomas Hodgkin: educator, scientist and philanthropist, a man not appreciated in his day and generation, and often later described as a failure.

Born in 1798 in Pentonville England into a Quaker family, little is recorded of his early life. His father, John Hodgkin, was a fashionable tutor of young ladies in the disciplines of mathematics and penmanship. Because of his family's religion, young Thomas adopted the manners and dress of the Society of Friends for the rest of his life.

For the study of medicine, he entered Guy's Hospital Medical School. After an undistinguished period as a medical student, he graduated in 1822 with his M.D.

In 1823, he journeyed to Paris for a year's study with the great René Laennec (1781-1826) and, upon his return to England, introduced the use of the stethoscope to the physicians at Guy's. He was one of the first physicians in England to believe in and use Laennec's wonderful new invention.

His Quaker upbringing made him a master of treating people rather than disease. He would attend all who sought his services but his disinterest in worldly matters made him careless about collecting fees.

"The tale is told that he sat up all night with a very wealthy man who was ill, and recovered. The patient was so grateful that he handed Hodgkin a blank cheque, telling him to fill it in for any amount he liked. Hodgkin entered ten pounds. The patient asked him why he put such a moderate amount. Hodgkin replied that he thought the drawer of the cheque looked as though he could not afford more. As a result, the patient was so angry that he never again asked Hodgkin for his services."

In a belief that more training in pathology would make him a better physician, Hodgkin became Curator of the Museum and Lecturer on Morbid Anatomy at Guy's. His enquiring and scientific mind led him to vastly extend and catalogue the Museum's collection of anatomical and pathological specimens, many of which are still present. At Guy's, he associated with many of the leading medical scientists of his day, including Richard Bright and Thomas Addison. He was the first pathologist in England to discuss gross pathological changes in view of their tissue aspects.

In 1827, Hodgkin published a paper "On The Retroversion of The Valves of The Aorta." Aortic insufficiency is usually associated with the name of Corrigan but Hodgkin's account of this condition precedes Corrigan's by three years. Today, this is generally regarded as one of Hodgkin's best publications.

Hodgkin published two papers in 1832, "On Some Morbid Appearance of The Absorbent Glands and Spleen." This was the first full description of lymphoma, although Malpighi had vaguely described the condition in 1666. In all, six cases were presented. Two of these have since been shown to be examples of other pathological conditions; however, it must be remembered that without the use of a microscope, some diagnostic confusion was inevitable and it is nevertheless a remarkable piece of work. This paper, regarded as vague and confusing at the time, remained in obscurity for thirty-three years until Sir Samuel Wilks published "Cases of a Peculiar Enlargement of The Lymphatic Glands Frequently Associated With Disease of The Spleen," a lucid description of lymphoma with many illustrative cases from several sources. At the time, Wilks had been studying "Lardaceous Disease" (amyloid degeneration). While examining lymph nodes, he noticed cases in which a chronic generalized lymphadenopathy was associated with splenomegaly and white masses in the

liver. He thought that he had discovered a previously unrecognized disease process until he learned from a statement of Richard Bright that Hodgkin had reported just such a condition more than three decades earlier. He acquiesced and named the condition "Hodgkin's disease." Many have thought since that "Wilk's disease" would be the more appropriate eponym.

In 1836, Hodgkin published "Lectures On The Morbid Anatomy of The Serous and Mucous Membranes," a monumental two volume treatise which greatly stimulated the study of tissue pathology in nineteenth century England.

For years Hodgkin had aspired to a clinical staff position at Guy's. In 1837, he again failed to obtain the post of assistant physician. Discouraged and despondent, he left his post in the pathology department and returned to private practice. For a short time he also lectured at St. Thomas's Medical School but soon decided to abandon the practice of medicine altogether and devote his life to various philanthropies and charitable works.

Hodgkin travelled to the East to work among the poor. In 1866 he died of bacillary dysentry in the city of Jaffa where his body is now buried.

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Recent Advances

Endolymphatic Radiotherapy

INTRODUCTION

Since 1961, Chiappa in Italy and Seitzman in Washington have employed I^{131}-labelled Lipiodal (Ethiodol) as an adjunct to the conventional treatment of primary or secondary tumours involving ilioinguinal, retroperitoneal or axillary lymph nodes. The purpose of this article is to present a clear picture of the current and possible future uses of endolymphatic radiotherapy.

MATERIALS AND METHOD

Ethiodol, an ethyl ester of poppy seed oil, and a conventional dye used in lymphangiography is rendered radioactive by replacing one of its inactive iodides with its isotope I^{131}. Prior to injection of the dye during lymphangiography, the patient is given Lugol's iodine to prevent uptake of the dye by the thyroid gland. After injection into the appropriate lymphatic channels, the radioactive contrast material reaches the appropriate nodes and emits β radiation. The effective half-life is 5 - 8 days. In spite of high levels of radiation (estimated to be 100,000 rads intranodally), little if any histologic effect of radiation is found beyond the capsule of the lymph nodes; the β particle has only a short penetrating ability of 2 millimeters. Koehler and his associates however investigated the fate of I^{131}-Ethiodol after endolymphatic injection into dogs and found the following:

(1) All of the injected medium did not remain confined to the lymphatics.

(2) A significant spillover to the lungs occurred and it was therefore thought that therapeutic amounts of I^{131} might expose the lungs to a high dosage of radiation.

USES

Currently, endolymphatic radiotherapy is being used as an adjunct to other forms of therapy in the following conditions with lymph node involvement:

(1) lymphomas
(2) testicular tumours—a direct injection is made into the lymph vessels of the spermatic cord
(3) carcinoma of the cervix
(4) carcinoma of the rectum
(5) certain tumours of the pelvis and kidney
(6) malignant melanoma

It has been shown that this technique of therapy is not effective if there is a large tumour mass present or if the lymph node is completely replaced by tumour, since the radioactive dye will bypass these areas. Thus, the best application is as a pre-operative procedure in the patient with early metastases. It is found that if opacification of lymph node tumours is insufficient or that some of the diseased groups are not being reached by the contrast medium, then external irradiation of these areas can be used in conjunction with the endolymphatic radiotherapy.

As an example of how this is employed clinically, Kinmonth's approach to the treatment of malignant melanoma will be listed:

(1) make the diagnosis of melanoma
(2) conventional wide excision of the primary lesion with skin grafts
(3) endolymphatic radiotherapy via the lymphatics draining the site of excision

(4) (a) if the nodes are clinically positive and radiologically negative, the patient is followed clinically and with serial lymphangiograms.

(b) if the nodes are clinically and radiologically positive with respect to metastases, a further block dissection is performed 4 - 6 weeks after the endolymphatic infusion. (This period of time allows radioactivity to decrease to a "safe level".) The dissection is guided by a lymphangiogram.

The latter method has the following advantages:

(1) more extensive treatment of the lymph tissue is effected—lymph nodes beyond the normal limits of a node dissection and which may contain microscopic-sized metastases are irradiated.

(2) any lymphoid tissue inadvertently left behind after the dissection will be less likely to contain viable tumour cells.

(3) spillage of viable tumour cells during dissection, leading to implantation, will be less likely to occur after previous irradiation.

In patients with clinically negative nodes, infusion will destroy micrometastases which are not suspected clinically. Thus, endolymphatic infusion is best used in those patients who have the greatest hope of survival. Fortner in 1963 reported on a large series of patients whose regional lymph nodes were clinically negative; however, after prophylactic block dissection, micrometastases were found in the nodes of 38% of the cases.

RESULTS

All investigators in the field have demonstrated a definite tumoricidal effect with the use of I^{131}-Ethiodol. The best series have come from Chiappa and his group in Italy, who have treated 500 patients with this technique since 1961. The following is a summary of the results he obtained in patients with lymphomas:

(1) A regression occurred in the majority of enlarged nodes. This began within 1 - 2 weeks after initiation of treatment, reached its maximum after about one month and has lasted more than one year.

(2) The therapeutic effect is almost proportional to the degree of opacification of the various lymph node groups.

(3) Remission of general symptomatology such as pain, meteorism and asthenia has also occurred.

(4) No untoward effects such as radiation sickness or damage to other organs, notably the lung and haematopoietic system, have been reported.

(5) Better results are obtained if the nodes involved are in the ilioinguinal group as opposed to the para-aortic nodes since difficulty in the filling of the latter nodes is encountered.

(6) The nodes involved in lymphosarcoma and reticulum cell sarcoma regress to a greater extent and more quickly than those in Hodgkin's disease and thus the results are better in the first two types of lymphoma.

One interesting and perhaps very useful aspect of endolymphatic radiotherapy has been reported by Kinmonth and his group in England. During the course of treatment of 50 patients with malignant melanoma, he noted that in several a relative and absolute lymphopenia lasting up to 5 months occurred, particularly when the ilioinguinal and para-aortic nodes were being treated. As a result, he has suggested that the para-aortic nodes may have a main function of producing lymphocytes for discharge into the general circulation via the thoracic duct and for this reason may be especially important immunologically as compared with other groups of nodes. In addition, he has advocated another possible use for this technique; namely as an alternative to the methods of immunosuppression now being employed in the early phase following transplantation. The current methods aimed at prolonging homograft survival are hampered by the fact that they produce leukopenia and are not selective in just destroying lymphocytes which are intimately concerned with graft rejection.

SUMMARY

In summary, the current status of endolymphatic radiotherapy has been reviewed. Its possible uses in increasing the survival of patients with primary or secondary tumour involvement of selected lymph nodes and in prolonging the function of homotransplants have not yet been determined; this requires further follow-up and research.

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Clinicopathological Conference

Intractable Diarrhea And Electrolyte Depletion In A Fifty-three Year Old Man

CASE PRESENTATION

A 53 year old, white male was admitted to the Toronto General Hospital July 12, 1961 for investigation of intractable diarrhea and severe debilitation which had persisted for 3 years prior to admission. The patient had been in good health until the summer of 1958 when he developed increasing frequency of bowel movements, varying from one a day to approximately 3-5 times a day. The stools were loose, brown in colour, and contained undigested food particles; there was no blood, mucus or melena. At this time the patient weighed 165 pounds (which was his normal weight), his appetite was fair, and he did not complain of dyspepsia. There was no nausea, vomiting or hematemesis. The patient drank about half a bottle of wine a day. There was no jaundice. Six months after the onset of diarrhea he noted increasing anorexia and abdominal distention which persisted for several months. Over the next six months the patient also noticed increasing weakness and weight loss. He now weighed 125 pounds. One year prior to admission to the Toronto General Hospital the diarrhea became more profuse with 2-12 loose bowel movements per day. At this time the patient frequently vomited undigested food particles and occasionally bile; however, there was no nausea. The stools were profuse, bulky, orange, slightly malodorous but never greasy, and they floated only when very liquid. The patient was admitted to the Oshawa General Hospital for investigation. X-ray studies of the gastrointestinal tract, glucose tolerance test, and sigmoidoscopy were all negative. He was discharged after 5-6 weeks, weighing 146 pounds, having some relief from his diarrhea, and with his appetite improved. Shortly after discharge, however, the diarrhea and vomiting recurred, now more frequently than before. The patient continued to lose weight. He was at this time on a high protein, gluten-free diet but he found that he could not adhere to this. Six months later the vomiting became more severe, occurring daily usually about ½ hour after meals. The abdominal distention returned, and the patient complained of vague, generalized abdominal pain. Approximately 3 weeks prior to admission to the Toronto General Hospital the patient was readmitted to the Oshawa General Hospital because of persistent vomiting which was at times projectile, severe diarrhea, and abdominal distention. The patient was then transferred to the Toronto General Hospital for further investigation. Functional enquiry was otherwise negative. Past medical history was non-contributory. The patient was said to be an alcoholic although he denied this. He had never travelled abroad, and had spent most of his life in Oshawa.

On physical examination the patient was thin and wasted, with a protruberant abdomen. He appeared chronically ill but was in no acute distress. The temperature was 98°F, respiratory rate 20/minute, pulse rate 92/minute, and blood pressure 80/60. No cyanosis or jaundice could be detected. There was no cardiomegaly but peripheral edema was present. The chest was clear to percussion and auscultation. The abdomen was distended and was tender in the epigastrium. There was also retrosternal tenderness. The liver edge was palpable 5 cm. below the right costal margin. It was firm, smooth, and non-tender. The spleen was not felt and no other organs or masses were palpated. Shifting dullness was present. There was no direct evidence of chronic liver disease. The bowel sounds were normal. The motor power was weak throughout, but there were no localizing signs and neurological examination was otherwise negative.

Initial blood work showed a hemoglobin of 13.5 gms %, the WBC was 12,800/cmm. with a normal differential, and the ESR was 94 mm/hour. The BUN was 45 mg %, the FBS was 96 mg %, and the total serum protein was 6.6 gms % (albumin 3.3 gms % and globulin 3.3 gms %). The serum phosphorus was 2.4 mg %, calcium 9.2 mg %, and alkaline phosphatase 18.0 King-Armstrong units. The serum sodium was 129 mEq/L, potassium 1.9 mEq/L, and chloride 91.7 mEq/L. Stool cultures were negative for pathogens, parasites and ova, and repeated sputum cultures were similarily negative for pathogens. Urinalysis, including bilirubin and urobilin, was negative. X-rays of the chest showed no abnormalities. Abdominal X-rays revealed marked gaseous distention of the large bowel and some segments of the small bowel; however, no evidence of mechanical obstruction could be seen. The wall of the small bowel appeared thickened due to the presence of free fluid in the abdominal cavity. An electrocardiogram showed evidence of hypokalemia.

The following laboratory data was obtained from the Oshawa General Hospital. Agglutinins for Salmonella and Brucella were negative. SGOT, CCF, alkaline phosphatase, and BSP excretion were all within normal limits. An oral xylose tolerance test was normal, as was a total fecal fat estimation.

Attempts were made to restore the patient's electrolytes to normal by vigorous intravenous therapy, with special attention to the potassium depletion. Large doses of oral potassium were given and the potassium level gradually increased to 2.4 mEq/L. over the next 10 days. The diarrhea continued but the patient was able to tolerate oral fluids and maintain himself in positive fluid and electrolyte balance.

On the thirteenth hospital day a barium enema was attempted. Following this the patient began to vomit and had massive watery diarrhea; he became very weak, unable to raise his legs off the bed, and his abdomen became more distended. Fluids, both by mouth and intravenous, were increased. The following morning the patient was confused, and there was diffuse tenderness over the whole abdomen. He was severely acidotic, hyperventilating, and had developed a sinus tachycardia. At this time the blood pH was 6.99, pCO_2 was 15 mm Hg, and the CO_2 content was 3.3 mEq/L. Treatment consisted of large doses of intravenous potassium and sodium bicarbonate. Twenty-four hours later the patient's condition was improved and the acidosis was controlled, but massive diarrhea persisted. The blood pH was 7.43 and the potassium was 5.4 mEq/L. Despite this apparent improvement the patient died suddenly the following morning, probably of a severe electrolyte disturbance which had occurred during the night. A post mortem examination was carried out.

DIFFERENTIAL DIAGNOSIS

The case history was presented to Dr. D. A. Stinson, of the Toronto General Hospital, and his discussion of the differential diagnosis follows:

Dr. D. A. Stinson:

Dr. William Boyd in his text book of Pathology, quoted from Goethe, "Was man weiss, sicht man" (What man knows, man sees). Also, what man *doesn't* know, man *doesn't* see.

This patient had a malignant condition that progressed inexorably to death over a 3 year period. His condition was unusual in many respects; so unusual that one would suspect a rare disease, or perhaps a rare variant of a disease.

Although he had a severe disturbance of the function of his gastrointestinal tract manifested by symptoms of both diarrhoea and vomiting that eventually led to severe inanition and electrolyte depletion, detailed examination of the tract failed to show a responsible lesion. Studies of stools and vomitus revealed no pathogens and no evidence of bleeding or inflammation. He was afebrile. This makes an inflammatory lesion very unlikely. Marked renal and hepatic dysfunction could cause a metabolic disturbance leading to diarrhoea and vomiting but liver and kidney functions appeared normal. The liver was palpable 5 cm. below the costal margin; this indicates an enlarged liver and must be considered in the diagnosis. The abdomen was distended, there was shifting dullness, and there was radiological evidence suggestive of ascites; this leads one to suspect disease involving abdominal peritoneum.

During the 2 weeks of his final hospital admission, a vigorous attempt was made to correct his markedly upset fluid and electrolyte balance but massive diarrhoea persisted and he died.

The data point to an intra-abdominal cancer causing ascites associated with severe vomiting and diarrhoea without evidence of direct tumor invasion of the bowel or stomach. It is extremely rare for a man to die of severe vomiting and diarrhoea with resulting electrolyte depletion with no evidence of a lesion in the gastrointestinal tract and no evidence of renal or liver failure.

If one *knew* that this condition could be brought about by a non-insulin-secreting, malignant tumor of pancreatic islet cells, one could have made the correct diagnosis prior to death. A liver biopsy or an examination of the cytology of the abdominal fluid might have confirmed the diagnosis.

Final Clinical Diagnosis: Non-insulin producing islet cell carcinoma of the pancreas.

The story goes that a Toronto professor of few words diagnosed correctly an extremely rare disease. Sir William Osler, who had also been the patient, asked the professor how he had come to such a brilliant conclusion. The answer, "What else could it have been?"

POST MORTEM FINDINGS

Gross

There was marked wasting of the body, especially in the extremities and the abdomen was distended. Pitting ankle edema was noted.

The stomach was distended with 1½-2 litres of thin, opaque, yellow fluid. The mucosa was normal with no evidence of atrophy, hypertrophy, or ulceration. No ascites was present. The intestines ballooned out of the abdominal cavity. They were filled with air and an orange-coloured fluid. The mucosal pattern in the jejunum was normal but in the ileum and colon it was flattened by a large amount of fluid. The liver weighed 2,550 gms. It was enlarged below the right costal margin and was studded with soft white umbilicated nodules which had replaced 30% of the liver substance. The intra and extra-hepatic ducts were normal and patent. The gall bladder was normal.

The pancreas weighed 90 gms. A discrete tumour was present in the tail. This tumour was identical in colour with the remaining normal pancreatic tissue. It was bilobular, hard, and cut with a gritty sensation. The cut surface was white with red streaks that ran through it in an irregular fashion. The coeliac lymph nodes were normal and the spleen was not infiltrated with tumour.

Microscopic

There was moderate atrophy of the mucosa of the stomach. No rugae were seen. The large and small intestines showed no abnormalities. The liver contained nodules of metastatic tumour (the cells were identical to those in the pancreatic tumour) but otherwise was normal. (See Fig 1).

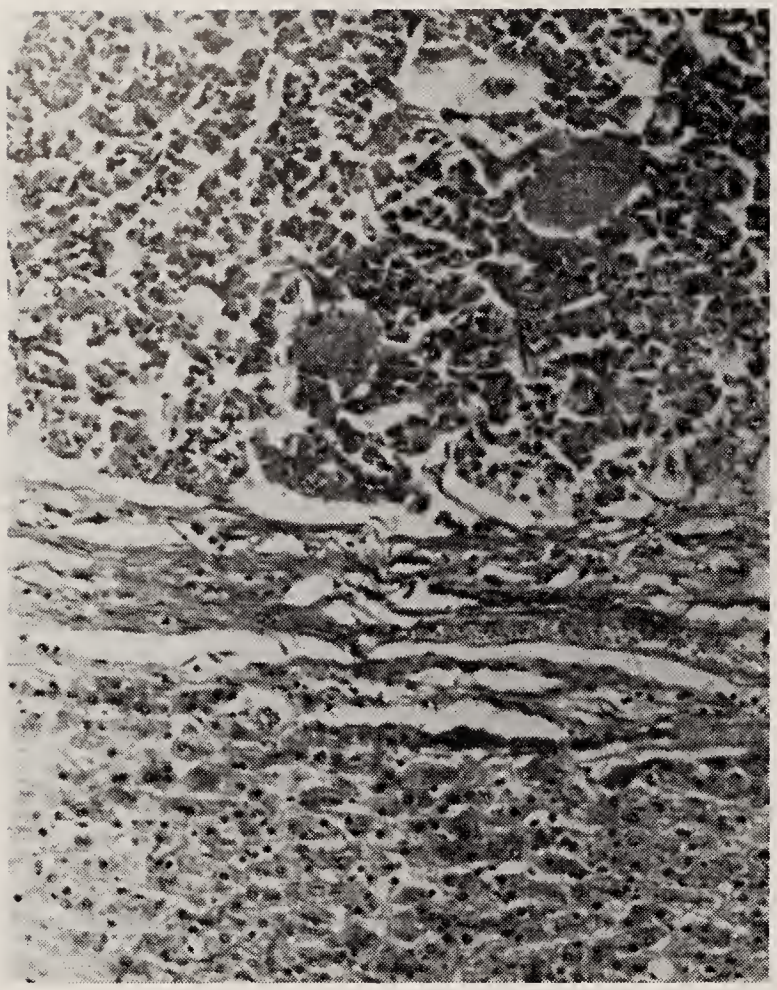

FIG. 1. (X160) Tumour cells have metastasized to the liver forming multiple secondary nodules (upper half shows tumour tissue).

The sections (H and E) of the pancreas showed two tumour masses, each invested within a fibrous tissue capsule. In the smaller nodule most of the tumour tissue was necrotic; however, in the larger nodule most was viable. This tissue was composed of clumps of tumour cells which were not arranged in any definite pattern. The stroma appeared scanty and was composed of thin sheets of connective tissue with some blood vessels. The tumour cells were large, with dark staining nuclei of irregular size and shape. The cytoplasm was eosinophilic, scanty, and moderately dense. Some mitotic figures were seen. The tumour cells had invaded the connective tissue capsule, breaking through it in some cases. Differential staining techniques failed to show whether the tumour cells were derived from alpha or beta cells. The pathological diagnosis was a non-insulin-producing islet cell carcinoma of the pancreas.

PANCREATIC ISLET CELL TUMOURS — DISCUSSION

Three distinct syndromes have been described in association with islet cell tumours of the pancreas. Hypoglycemia as a manifestation of tumours of the beta cell type has long been known. More recently the Zollinger-Ellison syndrome has been recognized as due to a non-beta islet cell tumour. A third group, although not well recognized, consists of cholera-like diarrhea and hypokalemia in association with a non-insulin-secreting islet cell tumour.

In 1927 Wilder *et al* reported the first case of a tumour of the islets of Langerhans which was associated with hyperinsulinism and hypoglycemia, thus establishing the concept that pancreatic tumours may have clinical significance as a result of secretory activity. Many cases of benign and malignant islet cell tumours with hyperinsulinism have been reported since that time.

In 1955 Zollinger and Ellison advanced the concept that a small number of islet cell tumours could be associated with an entirely different clinical syndrome. From their studies the diagnostic triad of fulminating ulceration of the stomach, duodenum, or proximal jejunum; marked gastric hypersecretion; and an islet cell tumour of the pancreas, has been defined. As well, in approximately 40% of the patients diarrhea was a prominent feature.

The pathophysiology of this syndrome has undergone intensive research over the last few years. It has been postulated that the tumour, consisting predominantly of alpha cells, secretes a substance that is a potent stimulator of acid secretion, presumably gastrin. Although gastrin itself has not been isolated from extracts of such tumours it has been shown that tumour extracts possess similar physiological properties. The diarrhea exhibited by these patients has been attributed to the enormous volume of HC1 secreted by the stomach with resultant irritation of the small bowel. Several authors have noted that the diarrhea could be controlled by nasogastric suction and that it recurred when the tube was withdrawn. Steatorrhea is also encountered due to the inactivation of pancreatic lipase by the low intraduodenal pH.

The syndrome of watery diarrhea and hypokalemia without peptic ulceration, in association with a non-insulin-secreting islet cell tumour was first established in 1958 by Verner and Morrison. Since that time a great deal of attention has been focussed on this condition and the metabolic disturbances which are produced. The importance of this syndrome lies not in the fact that it is a common clinical occurrence (only 15 cases have been documented in the English literature) but rather that it can be cured completely by removal of the tumour (if benign) and, therefore, should be considered in cases where no cause for long continued diarrhea and hypokalemia can be established.

The outstanding symptom in this group of patients is diarrhea which varies in duration and severity but is generally long standing and progressive. The stool contains little formed substance, is watery in consistency, and is inoffensive. Gastrointestinal bleeding is not seen. Weight loss and severe nausea and vomiting occur in the fulminant episodes of diarrhea. Symptoms due to hypokalemia and dehydration begin to appear as the diarrhea progresses. Muscular weakness and signs of impending stupor are evident. In untreated cases the

diarrhea and depletion of fluids and electrolytes become massive, leading inevitably to severe dehydration, hypokalemia, and death.

Roentgenographic studies, stool cultures, sigmoidoscopy, stool fat determinations, and urinary 5-hydroxyindoleacetic acid (5-HIAA) determinations are generally within normal limits.

The pathophysiology of this condition is by no means clearly established. The evidence to date suggests that the islet cell tumour produces a hormone-like substance which causes the diarrhea. It has been suggested that there is more than one hormone released by these non-insulin-secreting islet cell tumours. As mentioned previously, the hormone produced by the tumour in the Zollinger-Ellison syndrome is probably gastrin, or at least gastrin-like; however, it is postulated that a second hormone could be secreted which would produce the clinical picture of intractable diarrhea and hypokalemia without peptic ulceration. Assays of tumour extracts from such cases exhibiting the latter syndrome have failed to produce gastrin activity. As well, there have been well documented cases in which there has been evidence of gastrin-like activity only, evidence of diarrheogenic activity only, or evidence of both gastrin and diarrheogenic hormone secretion. The mechanism of production of diarrhea has been attributed to an oversecretion of normal intestinal fluids. Decreased intestinal absorption might also be a factor to be considered. In several cases the intestinal mucosal pattern has shown some bizarre alterations and in others the mucosal pattern has resembled that of sprue. There is no way of knowing how important the potassium deficiency may be in affecting the diarrhea, but this cannot be disregarded as a factor contributing to the disturbances of bowel function.

The actual islet cell comprising the tumour is difficult to identify. It was previously thought that the tumour consisted of predominently alpha cells, particularly those associated with the Zollinger-Ellison syndrome; however, because the histological methods for differentiating the cell types of the islets of Langerhans are not conclusive, classification of these tumours on the basis of cell origin is not adequate. The most that can be said of these tumours is that they are of the non-insulin-secreting or non-beta cell type.

With regard to treatment it has been found that prompt surgical removal of a benign tumour leads to complete remission of symptoms and subsequent cure. In cases in which the tumour is malignant and has metastasized, or in cases in which generalized hypertrophy and hyperplasia of the islets are present, the prognosis cannot be predicted with such accuracy.

In summary, a case of severe refractory diarrhea and hypokalemia in a patient with a non-insulin-secreting islet cell carcinoma of the pancreas was presented. Pancreatic islet cell tumours were briefly reviewed with special reference to the current theories of the pathophysiology involved.

R. E. Williams 6T9

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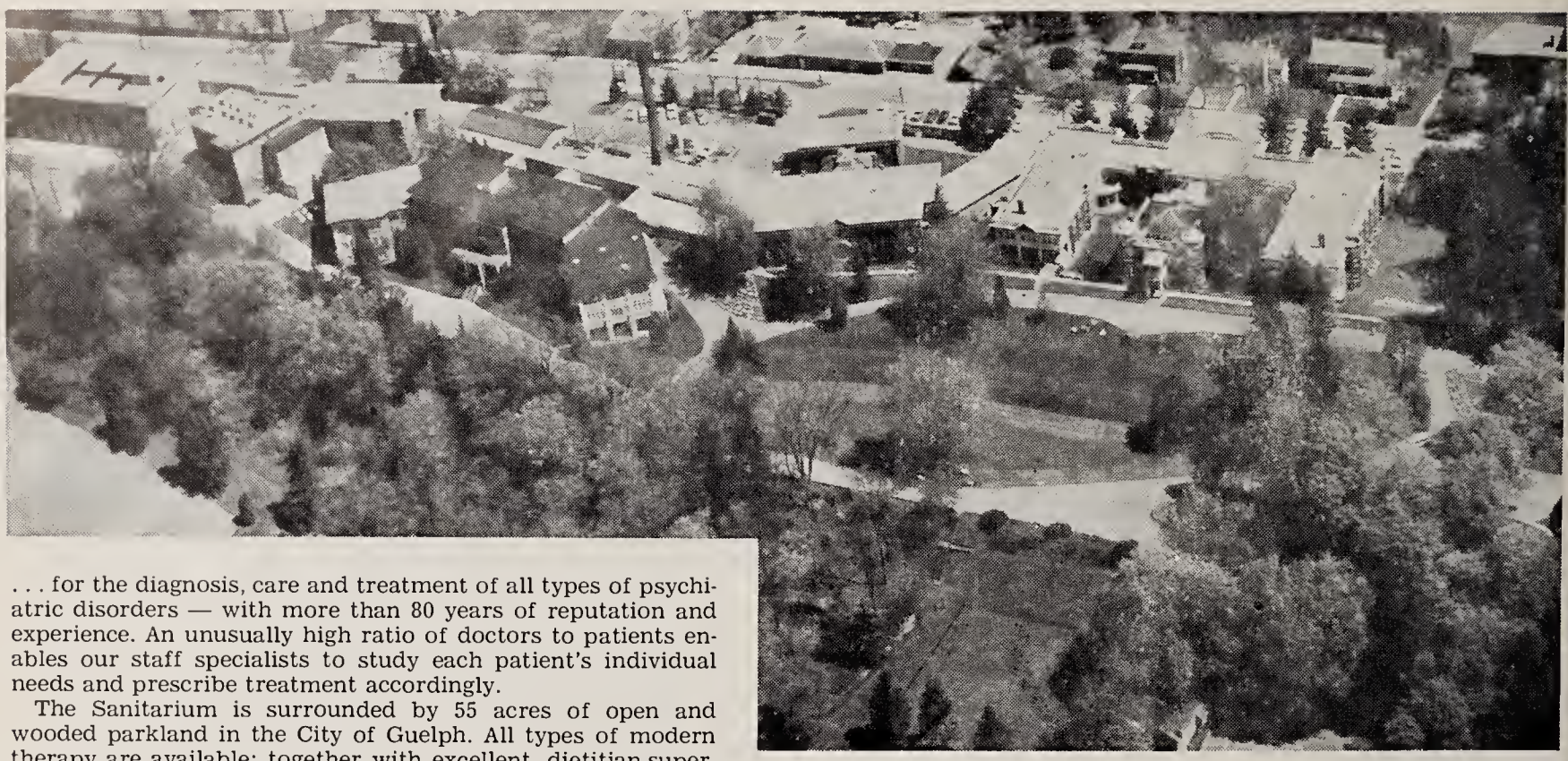

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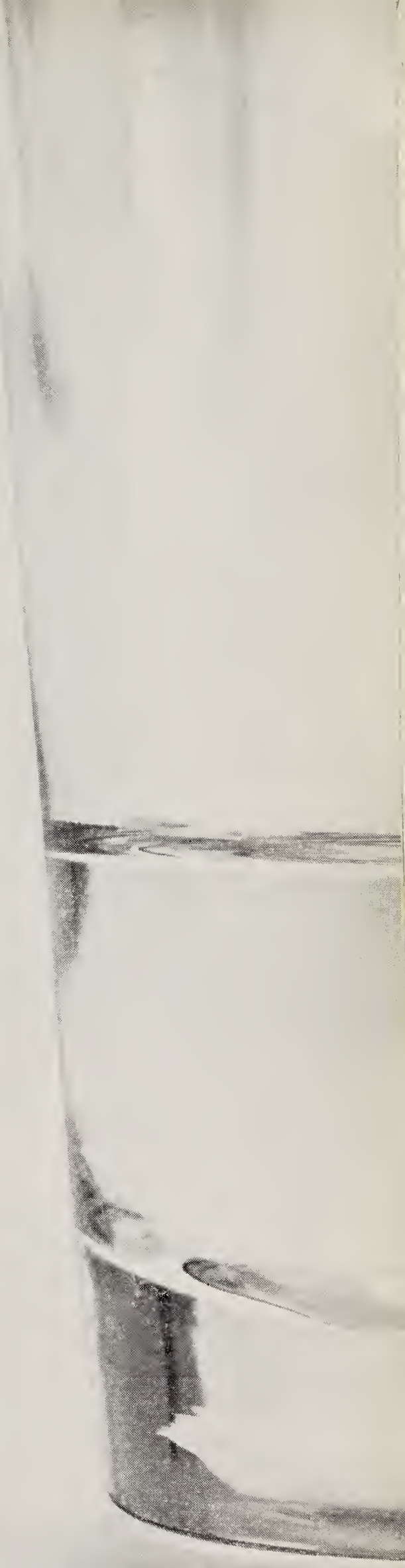

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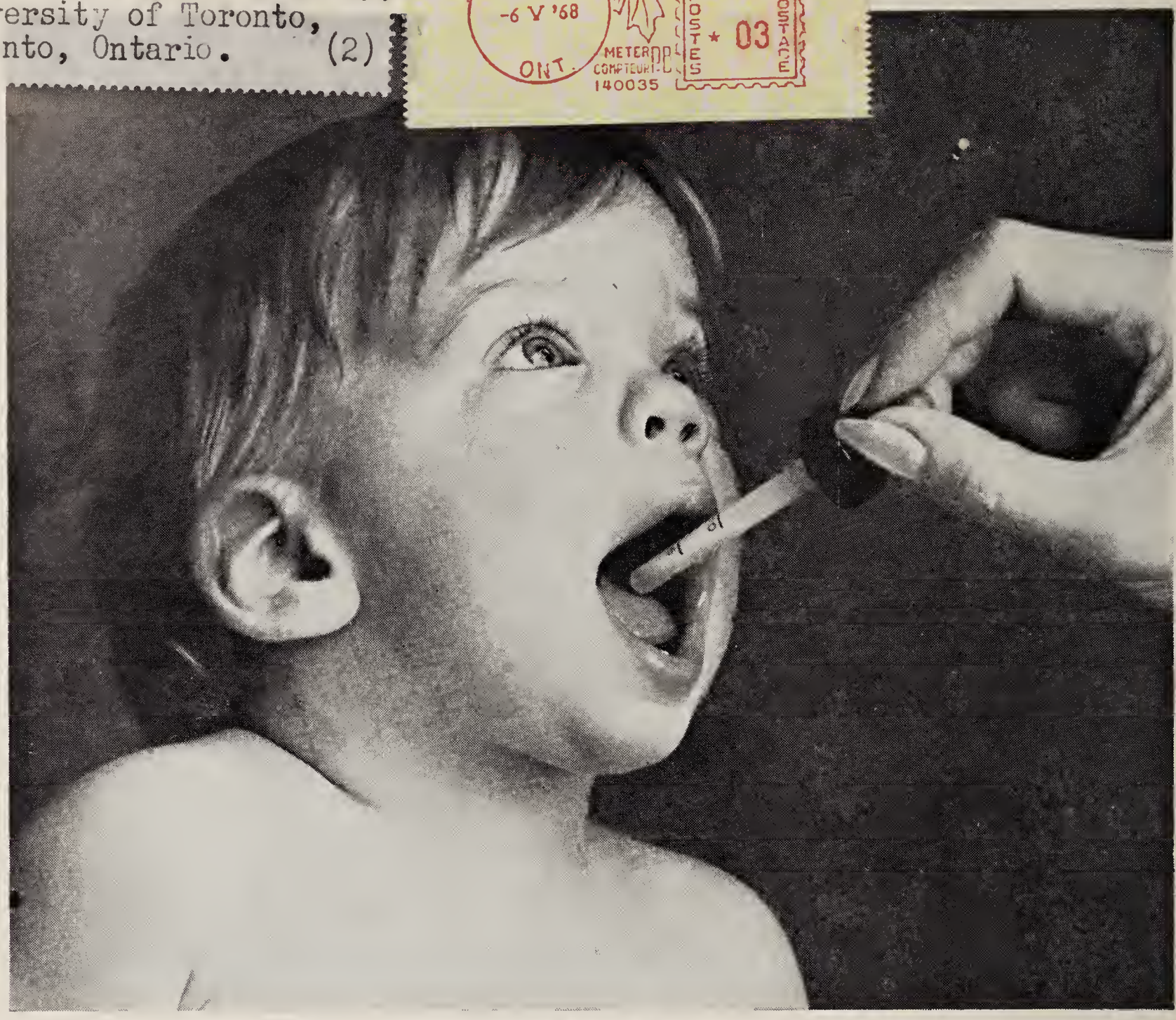

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